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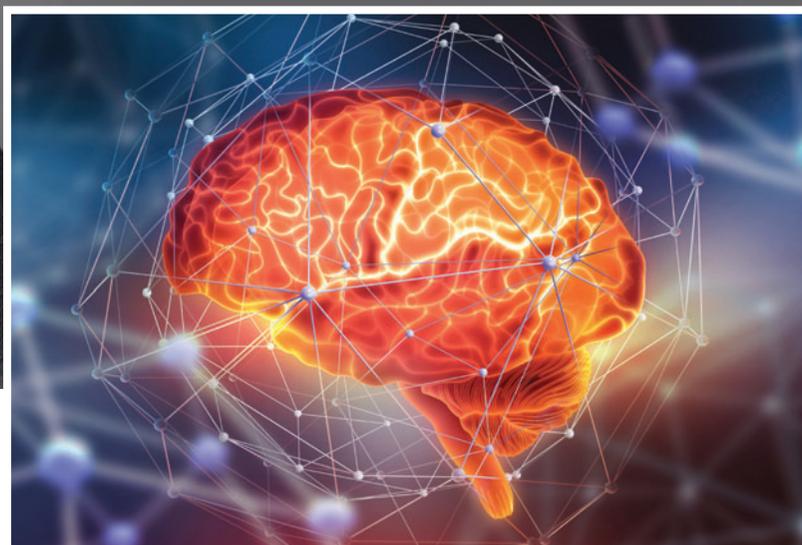


SANJAY ANEJA ON

Artificial Intelligence in Oncology

The Predictive Power of ‘Deep Learning’

‘AI may well transform oncology’



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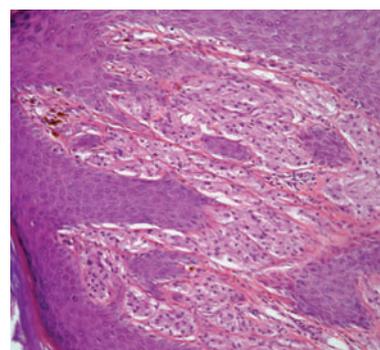
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Artificial Intelligence in Oncology: Current Applications and Future Directions

Benjamin H. Kann, MD, Reid Thompson, MD, PhD, Charles R. Thomas, Jr, MD, Adam Dicker, MD, PhD, and Sanjay Aneja, MD

Introduction

Artificial intelligence (AI), for years, has captured society's imagination and generated enthusiasm for its potential to improve our lives. Presently, AI already plays an integral role in our daily routines and our interactions with media, transportation, and communications. There is an increasing interest in the applications of AI in healthcare to improve disease diag-

nosis, management, and the development of effective therapies. Given the large number of patients diagnosed with cancer and significant amount of data generated during cancer treatment, there is a specific interest in the application of AI to improve oncologic care. In this review, we introduce the fundamentals of AI and provide an overview of its current applications, pitfalls, and future directions in oncology.

PERSPECTIVE

Tufia C. Haddad, MD, comments on AI to reduce burnout among oncologists on page 48.

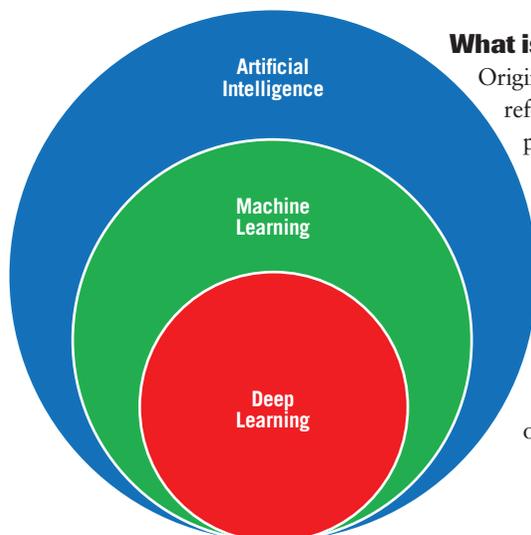


FIGURE 1 Relationship Between Artificial Intelligence, Machine Learning, and Deep Learning

What is AI?

Originally formalized in the 1950s, AI refers to the ability of a machine to perform tasks commonly associated with intelligent human behavior. [1] Including disciplines from both computer science and mathematics, AI can be considered a group of iterative, "self-learning" techniques, which discover relationships within data that can evolve and often be performed faster over time.

Machine Learning (ML): The Engine That Drives AI

A majority of the AI applications within healthcare involve the utilization of ML algorithms. As ML algorithms are

exposed to more training data, they are able to appreciate hidden patterns within the data which can then be used to perform a task without explicit programming.[2] There are dozens of ML algorithms that have been proposed over the past several decades, and the most traditional forms of ML, such as logistic regression, have proven themselves as valuable tools for general clinical oncology research.[3]

ML tasks are often broadly dichotomized into supervised or unsupervised learning. In supervised learning, a labeled dataset of inputs and outputs is used to train the ML algorithm. The algorithm attempts to learn a general rule that maps input to output. Supervised ML algorithms can learn patterns in data for categorical outputs (classification) and continuous data (regression). Conversely, unsupervised ML algorithms use unlabeled data, with the goal of discovering structure in the input data. Unsupervised ML algorithms are often used to simplify (dimensionality reduction) or organize (clustering) data.

In traditional ML tasks, there is often some pre-engineered organization of raw input data into features that are inferred to have an impact on output.

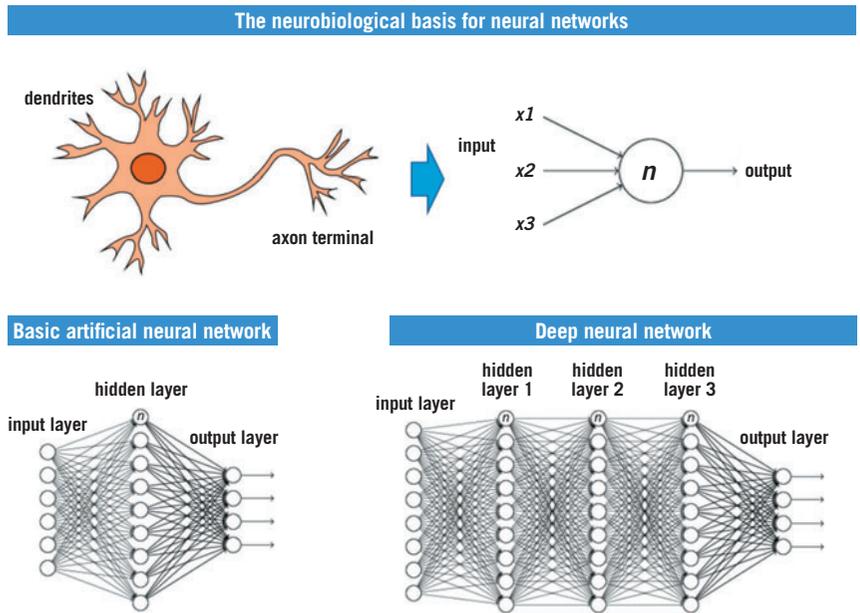
Artificial Neural Networks and Deep Learning (DL): The Wave Comes to Healthcare

One drawback of traditional ML algorithms has been the need for pre-engineered organization of raw input data into structured datasets. The inability of certain ML algorithms to use unstructured data from the point of generation has limited their utility in clinical practice. One ML algorithm well suited to analyze unstructured data is known as DL (Figure 1).

DL algorithms are often synonymous with AI. DL is a form of ML that uses layered "artificial neural networks" to develop sophisticated models with the ability to understand data at different levels of abstraction.[4] Artificial neural networks (ANNs) were inspired by human neurobiology and the ability of the brain to use cascading, varying, and layered combinations of neurons to learn complicated patterns with a hierarchy of progressively more complex features (Figure 2). Modeling the human neuron in computers yielded the basic design of early ANNs.[5]

While traditional ML algorithms used pre-engineered features to develop predictions, DL algorithms are able to learn the optimal features that best fit the data through the training process, avoiding the need to use pre-engineering, unstructured data. This ability has allowed DL algorithms to outperform traditional ML algorithms in many common AI problems, including image classification, natural language processing, and sequence prediction.[4,6,7] Accordingly, the number of research articles published involving deep learning in the medical field has skyrocketed over the past few years (Figure 3).

Due to this DL renaissance, AI has now generated significant attention in healthcare.[8–11] In oncology, DL has become a natural partner in the pursuit of precision medicine,[12–15] leveraging vast,



Adapted from: Nielsen M. Neural Networks and Deep Learning. Determination Press. 2015.

FIGURE 2 Neurologic Basis of Neural Network Architectures

n = neuron/node.

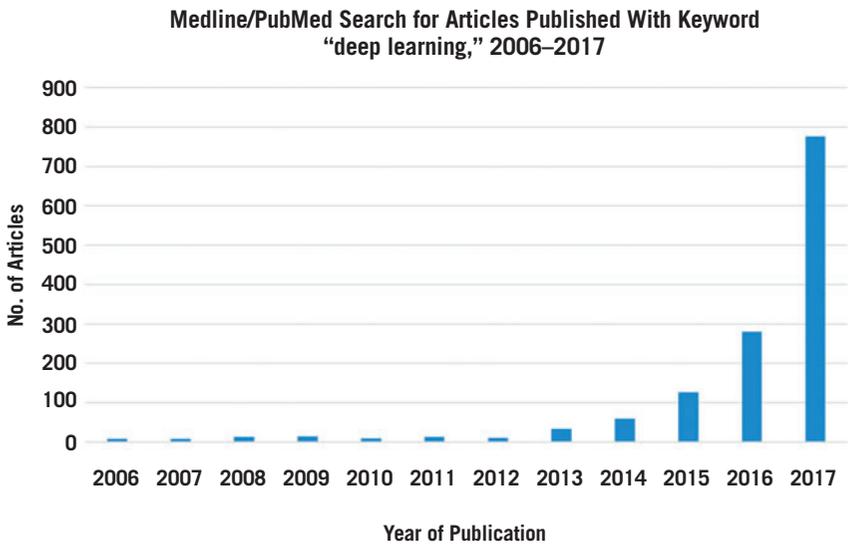


FIGURE 3 Rise in Deep Learning Publications

Number of articles published by year per Medline/PubMed search. Graph created with web resource: Alexandru Dan Corlan. Medline trend: automated yearly statistics of PubMed results for any query, 2004. <http://dan.corlan.net/medline-trend.html>.



PERSPECTIVE BY

Tufia C. Haddad, MD

Artificial Intelligence as a Solution to Burnout in Oncology

Developing applications of artificial intelligence (AI) and cognitive systems in oncology requires a collaborative, multidisciplinary effort that extends far beyond medicine and computer science. More than a few significant challenges, however, limit the translation of AI-related cancer research into meaningful clinical applications. Among these are the abilities to form partnerships across multiple industries, to gain equitable access to large volumes of annotated data, and to conduct unbiased training of machine-learning algorithms. The article by Aneja and colleagues provides a detailed overview of the evolving field of AI in oncology and serves as a primer for curious and reluctant oncologists alike, the vast majority of whom have not received formal training in data science.

While there has been hype that AI has the potential to replace doctors, early experience has suggested that AI can instead augment human intelligence, enabling doctors to perform with greater efficiency, engagement, and effectiveness. That said, a more credible, contemporary threat faces the oncology profession: unprecedented levels of burnout.[1] Although multiple factors have been associated with this state of stress, the ubiquitous involvement of computers in all aspects of medicine is recognized as a major driver. For example, while electronic health records (EHR), computerized prescribing, and order entry were established to improve quality and coordination of patient care, implementation of these systems has resulted in unintended consequences for providers: reduced efficiency and increased clerical and

cognitive burden.[2] During office hours, physicians spend almost 2 hours engaged in EHR and desk work for every 1 hour of direct patient face time,[3] and it is estimated that an additional 1.4 hours of EHR interactions occur daily outside of business hours.[4]

The EHR contains an enormous volume of data, and new data sources have the potential to generate a tsunami of additional patient data points. These include tumor genome sequencing reports, electronic patient-reported outcomes responses, patient online messaging, and patient-generated health data from apps and wearables. Integration of these data within the EHR and clinical workflows is currently suboptimal or lacking for most practices, furthering the rift between providers and their computers. Concurrent with this explosion of data is the frenzied pace of knowledge gains in oncology, including a record of 51 new agents or new indications for existing agents that were approved by the US Food and Drug Administration for cancer treatment in 2018. [5]

It has been recognized that much of the existing digital workload can be delegated to other care team members or to data abstraction and documentation specialists. Alternatively, technology may be exactly what is needed to solve our technology problem. Specifically, natural language processing (NLP), a branch of AI, can interpret, augment, and transform free text so that it can be represented for computation.[6] In medicine, it leverages the EHR, including its most valuable asset: the clinical note. NLP serves as the

engine for cognitive systems, but adoption of this technology requires expert training and supervision, as well as thoughtful implementation, with minimal disruption to clinical workflows.

Under these conditions, AI offers the potential for detailed EHR summarization in a single click, as well as clinical decision support at the point of care aligned with evidence-based care pathways. AI may also generate order sets, cancer registries, or personalized care plans for treatment or survivorship. Finally, it may provide optimized billing codes and quality/outcomes reporting for programmatic assessments and regulatory mandates. While extraordinary investments have aimed to create AI applications for cancer risk prediction, diagnosis, and treatment, perhaps an equally noble goal would be to develop the NLP capabilities of cognitive systems to eradicate the growing mindless hours spent navigating the EHR, thereby allowing oncologists to do what they do best: provide the highest level of cutting-edge, patient-centered care to those facing cancer.

FINANCIAL DISCLOSURE: Dr. Haddad has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➤ For references visit cancernetwork.com/AI-in-oncology

Dr. Haddad is a Medical Oncologist, Chair of the Breast Medical Oncology practice, and Chair of Health Information Technology in the Department of Oncology at the Mayo Clinic in Rochester, Minnesota.

heterogenous datasets to better diagnosis disease burden, predict patient outcomes, and tailor management. AI can also be coupled to a multitude of emerging mobile health interfaces, such as smartphone apps and wearable devices, to develop “digital biomarkers” that can explain, influence, and predict clinical outcomes. In the following sections, we will delve into current AI applications in oncology, their limitations, and future implications.

AI and Cancer Imaging Seeing better with convolutional neural networks

Image analysis has proven to be among the most effective methods in which AI has impacted society. AI powered by DL algorithms has provided us self-driving vehicles, mobile check deposit, and multiple other useful technologies. Given the large amount of digital imaging data present within medicine, there is increasing excitement about the application of similar techniques to imaging within oncology (Table 1).

This revolution in image analysis was catalyzed by the development of a particular DL architecture, the Convolutional Neural Network (CNN). CNNs analyze pixel-level information from images. The added benefit of CNNs compared to other DL configurations is the ability to account for orientation of the pixels in relation to one another. This effectively allows the CNN to appreciate lines, curves, and eventually objects within images. CNN-based models have recently been shown to be equivalent to humans in picture classification and object detection.[6,16]

Clinical photographs

One of the initial papers highlighting the promise of DL in cancer imaging was in identification of skin cancer based on skin photographs.[17] The CNN trained on 130,000 skin images was able to classify malignant lesions with higher sensitivity and specificity than a panel of 21 board-certified dermatologists. Practical applications of detecting skin pathology utilizing patients as the generator of imaging input data

TABLE 1 Applications of Artificial Intelligence in Imaging

Author	Disease Site	AI Task	Method	PMID
Chang et al[32]	Brain	Brain tumor classification and genetic mutation prediction (MRI)	Deep Learning	29167275
Ribli et al[29]	Breast	Tumor detection and classification (mammogram)	Deep Learning	29545529
Lu et al[77]	Colorectal	Lymph node identification and classification (MRI)	Deep Learning	30026330
Wang et al[19]	Colorectal	Polyp identification and classification (endoscopic)	Deep Learning	(DOI) 10.1038/s41551-018-0301-3
Kann et al[31]	Head and Neck	Lymph node classification and histopathologic prediction (CT)	Deep Learning	30232350
Nikolov et al[78]	Head and Neck	Tumor auto-segmentation (CT)	Deep Learning	arXiv:1809.04430
Coudray et al[38]	Lung	Histopathologic classification and genetic mutation prediction (histopathology)	Deep Learning	30224757
Liao et al[79]	Prostate	Prostate gland auto-segmentation (MRI)	Deep Learning	24579148
Fehr et al[80]	Prostate	Tumor classification and Gleason Score prediction (MRI)	SVM / Adaptive Boosting	26578786
Esteva et al[17]	Skin	Skin lesion classification and histopathology prediction (photograph)	Deep Learning	28117445

PMID = PubMed identifier; SVM = support vector machine.

has evolved.[18] Further use of CNNs to classify digital photography has been in the automatic detection of polyps during colonoscopy. One particular study highlights that CNNs can be used for not only image classification, but also to detect regions of clinical importance. Researchers found that CNN, which was trained on colonoscopic images from 1,290 patients, had a 94% sensitivity in polyp detection.[19]

Radiographic imaging

Given one of the most effective applications of AI techniques has been in the

field of computer vision, there is naturally excitement in the field of radiology, where there exist a number of digitized images. The goals of these AI algorithms have ranged from assisted diagnosis to outcome prediction.

AI algorithms have been found to be effective in streamlining cancer screening and detection. Automated lung nodule detection and classification has attracted significant attention and formed the basis of the 2017 Kaggle Data Science Bowl, an international competition for ML scientists.[20] Several successful CNN-based

TABLE 2 Applications of Artificial Intelligence in Clinical Outcome Prediction

Author	Disease Site	AI Task	Method	PMID
Lao et al[81]	Brain	Survival prediction using MRI images	Deep Learning	28871110
Yousefi et al[82]	Breast / Brain / Renal	Survival prediction using genomic and clinical data	Deep Learning	28916782
Zhen et al[46]	Cervical	Acute radiotherapy toxicity prediction	Deep Learning	28914611
Bibault et al[34]	Colorectal	Chemoradiation response using CT images	Deep Learning	30135549
Aerts et al[83]	Head and Neck / Lung	Disease outcome prediction and classification using CT images	Deep Learning	24892406
Chaudhary et al[84]	Liver	Survival prediction using RNA and miRNA sequencing and methylation data	Deep Learning	28982688
Sun et al[35]	Lung	Immunotherapy response using CT images and histopathology	Elastic-net Linear Regression	30120041
Miotto et al[39]	Multiple	Patient disease classification and outcome prediction	Deep Learning	27185194
Pella et al[42]	Prostate	Acute radiotherapy toxicity prediction	Artificial Neural Net / SVM	21815361
Carrara et al[43]	Prostate	Late radiotherapy toxicity prediction	Artificial Neural Net	30092335

PMID = PubMed identifier; SVM = support vector machine.

models resulted from this competition and other research groups, demonstrating accuracies in the 80% to 95% range and showing promise for lung cancer screening.[21–26] Additionally, CNNs have been shown to be successful in segmenting tumor volumes, which may have implications for radiotherapy treatment planning.[27] Improvement of breast cancer screening with AI has also been an active area of investigation, with its own data science competitions,[28] resulting in a CNN algorithm able to detect breast malignancy with a sensitivity of 90%.[29,30]

AI has also shown promise in detecting radiographic anatomic features of

malignancies that goes beyond what can be reliably achieved by clinicians. While extranodal extension (ENE) of tumors in the head and neck cancer lymph nodes has been notoriously difficult to diagnosis radiographically by clinicians, a CNN-based model showed >85% accuracy in identifying this feature on diagnostic, contrast-enhanced CT scans.[31] Identification of ENE has high importance in prognostication and management for head and neck cancer patients, and thus this model shows promise as a clinical decision-making tool.

Going further than anatomic characterization, AI has shown promise in the burgeoning field of radiogenomics,

where radiographic image analysis is used to predict underlying genotypic traits. This has recently been demonstrated using CNNs on brain MRIs of patients with low-grade glioma. CNNs have been able to predict both *IDH* mutation and *MGMT* methylation status with 85% to 95% and 83% accuracy, respectively, based on raw imaging data alone.[32,33]

DL also has the potential to predict response to treatment based on imaging findings. Recently, a CNN model showed success in predicting complete response to neoadjuvant chemoradiation with 80% accuracy.[34] Additionally, a radiomics signature using extracted features from CT data and a ML algorithm were able to predict underlying CD8 cell tumor infiltration and, remarkably, response to immunotherapy for a variety of advanced cancers.[35]

Digital pathology

The increasing digitization of histopathologic tumor specimen slides provides a robust 2D image suitable for DL analysis. DL CNN algorithms have now been shown to diagnose breast cancer metastasis in lymph nodes with at least equivalent performance compared to a panel of pathologists, and in a more time-efficient manner.[36] DL has also been shown to be useful in automated Gleason grading of prostate adenocarcinoma Hematoxylin and Eosin–stained specimens, with a 75% rate of agreement between the algorithm and pathologists.[37]

DL algorithms have also gone a step further than pathologic diagnosis automation and have been used to characterize the underlying genotype-phenotype correlation within a tumor specimen. Using raw input data consisting of digitized formalin-fixed, paraffin-embedded tissue from lung cancer biopsies, a CNN was trained to predict six different genetic mutations (*STK11*, *EGFR*, *FAT1*, *SETBP1*, *KRAS*, and *TP53*), establishing that genotypic information may be gleaned from histopathologic architectural patterns.[38] These methods may assist pathologists in the detection of cancer gene muta-

tions and may be cost-effective compared to direct mutational analysis.

AI and Clinical Outcomes

Within clinical oncology, AI has increasingly been applied to harness the power of the electronic health record (EHR) (Table 2). Specifically, AI-based natural language processing techniques have shown promise in predicting the development of diseases across large healthcare systems. A notable example from a group at Mount Sinai, a DL-based AI algorithm modeling EHR, was able to predict the development of a variety of diseases with 93% accuracy overall, including cancers of the prostate, rectum, and liver.[39]

There has additionally been interest in using DL to predict cancer treatment toxicity. Recently, a CNN approach was used to predict side effects of polypharmacy combinations based on databases of protein-protein and drug-protein interactions.[40] This study led to the discovery of at least five novel drug-drug interaction predictions, which were subsequently found to have supporting literature evidence. Use of AI to predict radiotherapy toxicity has generated significant interest over the past few years.[41] Basic neural networks, CNNs, and other ML methods have been explored, using clinical and dosimetric data to predict urinary and rectal toxicity resulting from prostate radiotherapy results,[42–44] hepatobiliary toxicity after liver radiotherapy,[45] and rectal toxicity for patients receiving radiotherapy for cervical cancer.[46]

AI and Translational Oncology

Translational oncology is an area where AI is beginning to emerge. Over the past decade, there has been an expansion of biological quantitative or “-omic” data. Given the complexities and heterogeneity within this data, the use of DL in analysis has been appealing. DL neural networks have been utilized to predict protein structure,[47] classify cells into a distinct stage of mitosis,[48] and even predict the future lineage of progenitor cells based on microscopy images.[49]

TABLE 3 Applications of Artificial Intelligence in Translational Oncology

Author	AI Task	Method	PMID
Feng et al[85]	Drug-target interaction strength prediction	Deep learning	arXiv:1807.09741
Preuer et al[86]	Anti-cancer drug synergy prediction	Deep learning	29253077
Zitnik et al[40]	Polypharmacy side effect prediction	Deep learning	29949996
Han and Kim et al[52]	Peptide-MHC binding prediction	Deep learning	29281985
Eulenberg et al[48]	Cell cycle reconstruction and disease progression prediction	Deep learning	28878212
Aliper et al[87]	Transcriptomic-based drug repurposing prediction	Deep learning	27200455
Menden et al[51]	Cancer cell drug sensitivity prediction	Artificial neural network/random forest	23646105

MHC = major histocompatibility complex; PMID = PubMed identifier.

Drug development and repurposing has become an attractive target for DL. One group used DL ANNs trained on transcriptomic response signatures to drugs to predict with high accuracy the likelihood of failure of a clinical trial of over 200 example drugs.[50] Another used an ANN to predict cancer cell sensitivity to therapeutics using a combination of genomic and chemical properties.[51] CNNs have also been employed to predict peptide-major histocompatibility complex binding,[52] which may have implications for oncologic immunotherapy development. See Table 3 for a summary of applications of AI in translational oncology that have been researched.

AI and Clinical Decision Making

Given the increasing amount and pace of published research, clinical trial enrollment, drug development, and biomarker discovery in oncology in recent years, there is more opportunity than ever for AI to assist in synthesizing this data and to guide decision-making. There are several commercial applications in development that

utilize DL and natural language processing to this aim.[53] These applications are being designed to link patient data to clinical trial databases and to match patients to appropriate clinical trials nationwide. Another algorithm utilizes ML to select the appropriate investigational drugs in development for a given patient. There has also been interest in utilizing AI coupled with patient data and national treatment guidelines to guide cancer management, with the most prominent example being IBM’s Watson for Oncology (WFO). WFO has demonstrated high concordance with tumor board recommendations for breast cancer patients, though has fallen short in other areas of oncologic decision-making.[54,55] While this area of AI application is in its nascent stages, performance continues to improve, and there is great potential to improve clinical practice.

AI Limitations and Future Directions

Proving generalizability and real-world applications

While AI is rapidly being incorporated into oncologic research, work remains to be done to translate these studies into

real-world, clinically meaningful applications. One of the biggest barriers is in external validation and proving generalizability of DL applications. Given the complexity of neural networks and the extremely large number of parameters (often in the millions), there is a high tendency for neural networks to create overfitted models that do not generalize across different populations. Additionally, because there is a significant amount of heterogeneity of medical data across institutions, multiple external validation sets may be required to prove the performance of an application.[56]

Data access and equity

Directly contributing to this problem of overfitting are limitations with data access and quality. DL neural networks, more than any other ML algorithm, require large amounts of data. This can pose a problem in healthcare when attempting to apply AI to disease processes with less prevalence. Furthermore, data is often siloed within individual institutions. Contributing to this relative data drought are concerns with transmission of protected patient health information, along with lack of data-sharing infrastructure to link institutions, heterogeneity and incompleteness in the collection of data, and competition between institutions. These obstacles are beginning to be addressed, with more and more emphasis on streamlined data capture,[57] and a number of multi-institutional data-sharing agreements[58–61] Guidelines have been proposed to support FAIR (findable, accessible, interoperable, reusable) data use,[62] and there are now opportunities for research groups to publish their data itself, which may incentivize openness.[63]

Interpretability and the black box problem

One of the central limitations to adoption of AI in healthcare is the concern that these models, despite regularly achieving high performance, are somewhat opaque. For instance, a DL model may correctly



Groundbreaking research in DL neural networks is poised to make a practice-changing impact on oncologic care.

predict that a patient will develop pancreatic cancer based on his past 2 years of EHR data, but why did it make that prediction? At the present, we are limited in our ability to determine the precise logic behind DL-based predictions. This is often referred to as the “black box” problem.[64] In medical practice, it has traditionally been essential in clinical decision-making to know the rationale for each decision. Traditional ML algorithms, like linear regression, have limited ability to model complex relationships, but offer this easy interpretability—in these algorithms, we have a set of pre-defined features and the resulting feature weights that characterize their effect sizes. In contrast, DL utilizes unstructured input data, and the bulk of knowledge generation occurs within the hidden layers. It thus becomes difficult to determine which specific characteristic(s) of the input data contributed to the outcome. This interpretability challenge has large implications for adoption of AI-based algorithms in healthcare, both from practitioner and regulatory perspectives.[65–68]

Tackling the black box problem has now become a major focus of research.[69] In AI image analysis algorithms, several methods have been developed, including feature visualization, saliency maps, class activation mapping, and sensitivity analyses, where certain parts of the image are hidden to the effect on prediction.[70] While these methods have advanced over the past few years, further work is needed to better elucidate the decision-making logic with deep neural networks.

Education and expertise

To successfully merge AI with clinical oncology and maximize its impact, there are knowledge gaps that need to be addressed. Currently, physicians receive little training in data science and ML, limiting their ability to understand DL mechanisms, adopt algorithms appropriately, and conduct research.[71] Similarly, most data scientists have little experience with oncologic workup and management, limiting the ability to identify important and suitable clinical use cases. Further collaboration should be pursued between clinical oncologic departments and bioinformatics and data science divisions, and strategic partnerships with technology firms should be formed where appropriate.

Promoting AI in Oncology: Professional Societies and National Initiatives

In response to these challenges, several national professional societies have launched initiatives to bridge these knowledge gaps and promote the dissemination of AI in oncology.

American College of Radiology (ACR)

The ACR has founded a Data Science Institute (ACR-DSI) with the mission of collaborating with radiologists, industry, and government agencies to facilitate the development of AI in imaging.[72] Within the ACR-DSI are several core goals: 1) providing standards for measuring performance of AI algorithms (“Touch-AI”), 2) independent, external validation of algorithms and navigating the regulatory landscape (“Certify-AI”), and longitudinal, prospective evaluation of deployed algorithm performance (“Assess-AI”). The ACR-DSI has additionally set up a series of use cases for recommended AI imaging applications with unmet clinical need.

American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO)

ASCO has launched a big data initiative

named CancerLinQ, in partnership with oncologists, industry, and academia, with the goals of real-time quality of care tracking and treatment evaluation, as well as knowledge dissemination to oncologists in user-friendly ways.[73] The initiative's backbone is a constantly growing database of de-identified patient information that can be mined and analyzed. In 2017, ASTRO partnered with CancerLinQ to provide radiation oncology expertise and uses for the database. In addition, Big Data Analytics and Bioinformatics is one of the core initiatives of the ASTRO Research Agenda for 2018.[74]

National Institutes of Health (NIH)

As part of the NIH Common Fund, the Big Data to Knowledge (BD2K) initiative was launched to support the research and development of tools to integrate big data and data science into biomedical research. [75] One of the central components of the initiative involves leveraging existing national datasets, such as the Library of Integrated Network-based Cellular Signatures (LINCS) and The Cancer Genome Atlas (TCGA), and applying ML techniques to discover patterns in the data that may result in heretofore unknown compounds for cancer therapeutics.[76]

Conclusions

Over the past decade, AI has undergone a reawakening. Due to an explosion of electronic data, advances in technological infrastructure, and groundbreaking research in DL neural networks, AI is poised to make practice-changing impacts on the medical field and oncologic care.

Artificial Intelligence: Terms and Definitions

Term	Definition
Machine learning	The ability to learn and improve from data without being explicitly programmed
Deep learning	A type of machine learning that uses layered neural networks with large amounts of raw data
Raw data	Unprocessed data (eg, EHR, imaging, text)
Supervised learning	Learns patterns from pre-labeled output data
Unsupervised learning	Learns patterns from unlabeled data
Classification	Machine learning to separate data into categories (eg, benign vs malignant)
Regression	Machine learning to predict from data a continuous numerical output (eg, percentage risk of metastasis)
Dimensionality reduction	Machine learning to create simplified representations of complex data
Clustering	Machine learning to separate data with similar characteristics into distinct bins or categories

EHR = electronic health record.

At present, AI has shown promise in improving cancer imaging diagnostics and treatment response evaluation, predicting clinical outcomes, and catalyzing drug development and translational oncology. Obstacles remain—such as validation and proving generalizability, concerns over interpretation, and the widening knowledge gap between clinical and data science experts. If we can address these challenges, AI has the potential to trans-

form oncology, harnessing the power of big data to drive cancer care into the 21st century and beyond. ■

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➤ For references visit cancernetwork.com/AI-in-oncology



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Inadequate Awareness of and Participation in Cancer Clinical Trials in the Community Oncology Setting

Mehmet Sitki Copur, MD, FACP

Introduction

Participation in cancer clinical trials provides patients access to the latest, most promising investigational interventions, as well as close monitoring of care. However, only 3% to 5% of eligible adult cancer patients are enrolled in clinical trials. This results in delays in the progress of cancer research, as well as increased costs for improving and disseminating effective cancer treatments.[1] The reasons for low rates of clinical trial participation are numerous. Trials may not be available to those willing to participate; when they are available, patients are often excluded because they do not meet trial eligibility criteria.[2-4] In the United States, available data on the demographics of oncology patients participating in clinical trials show that those who do enroll are more likely to be younger, male, and Caucasian, and to have later-stage cancer, compared with those not enrolled in trials.[5-8] These trends are also true of clinical trials conducted in other countries.[9]

Cancer-related clinical research and clinical trials have traditionally been conducted at well-established academic medical centers, while 85% of cancer patients are diagnosed and treated at local, community-based clinical practices. Therefore, community-based cancer re-

search is critical in advancing cancer care for the large, diverse patient population that receives treatment in a variety of local healthcare delivery settings. In addition, participation of community oncologists and primary care physicians in cancer prevention, control, and treatment trials significantly helps facilitate the translation of research advances into practice.

Support for Community-Based Research Community Clinical Oncology Program (CCOP)

For the last 4 decades, the National Cancer Institute (NCI) has acknowledged the importance of community-based oncology research through several initiatives and programs for community practices. Historically, the significance of community-based research was solidified in 1982, when the NCI initiated the CCOP.[10] This collaborative partnership between research institutions and community-based physicians helped to facilitate phase III cancer prevention, control, and treatment trials in the community-based practice setting. The CCOP was designed to disseminate and implement advances in cancer care by linking cancer investigators and academic centers to community-based practices, thus expanding access to clinical trials and

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discusses patient barriers to trials
on page 56.

promoting cancer treatment innovations within the community populations that otherwise might not have had access.

NCI Community Cancer Centers Program (NCCCP)

Despite these efforts, community-based cancer research continued to face challenges as a result of the era of emerging science, technology, genomics, and molecular-targeted therapy, as well as a rapidly changing healthcare environment. In 2007, the NCI further expanded its community-targeted efforts by launching the NCCCP, a public-private partnership with 21 community hospitals in 16 states. [11] The goals of the NCCCP were to enhance access to and improve the quality of cancer care by expanding the infrastructure to support a platform for basic, clinical, and population-based research, as well as informatics, biospecimen collection, and cancer care disparities in community hospitals. Self-reported data collected at NCCCP sites between 2007 and 2010,

supplemented with data from the NCI Cancer Therapy Evaluation Program, showed that the availability of phase III trials and patient accrual increased by 16% and 133%, respectively, at NCCCP sites, compared with 8% and 30% nationally. In addition, enrollment of racial and ethnic minorities in oncology trials increased by 82%, from 83 to 151 patients; the accrual of patients aged 65 years or older in oncology trials also rose by 221%, from 200 to 641 patients. The exact changes in trial portfolios and accrual differed by sophistication of the site and by prior experience conducting clinical trials at the site.[12]

NCI Community Oncology Research Program (NCORP)

In 2014, the NCI initiated a new community-based program, the NCORP, to align with and replace the CCOP and NCCCP programs. The goals of the NCORP are to support clinical trials on cancer control, prevention, treatment, and screening in the community setting, as well as to expand the scope of research to include cancer care delivery. The NCORP initiative emerged around the same time as two other significant changes: 1) the transformation and condensing of nine longstanding NCI Cooperative Group programs into four new groups under the National Clinical Trials Network, and 2) the implementation of the NCI Central Institutional Review Board. Both of these changes helped to provide easier access to all NCI Cooperative Group clinical trials with some reduced regulatory burden. In a study conducted at St. Francis Cancer Treatment Center in Grand Island, Nebraska, we found that participation in both NCI programs, NCCCP and NCORP, positively impacted clinical trial-related activities and expanded research, with enhanced access to quality cancer care. In addition, NCORP provided a robust Cooperative Group trial linkage, resulting in a record-high clinical trial portfolio.[13]

Barriers to Participation Inadequate funding

Funding is one of the largest challenges

facing Cooperative Group clinical trials. Namely, there has been a growing discrepancy between the actual cost of Cooperative Group trials compared with the amount of funding received from the NCI. In addition, the routine per-case reimbursement for Cooperative Group trials has remained stagnant at around \$2,000, despite an increase seen in the actual cost over time to approximately \$6,000.[14] In a 2010 American Society of Clinical Oncology (ASCO) survey of 500 clinical trial sites, 33% indicated that they planned to limit their involvement in Cooperative Group trials, and 75% cited inadequate funding as a reason for doing so.[15] To address these concerns, the NCORP intends to award \$74.5 million of funding in fiscal year 2019 to be used for up to seven 6-year research projects. While application budgets are unlimited, the focus should reflect the needs of diverse patients in a variety of community oncology settings, including rigorous studies on cancer prevention, control, screening, care delivery, and quality of life.[16]

Systems-based challenges

As strong and, to some extent, as successful as these NCI programs have been, the national clinical trial participation rate of 3% to 5% remains unchanged, with mounting barriers to enrollment. In addition to regulatory and bureaucratic requirements, administrative, financial, and organizational challenges beyond the control of participating hospitals and clinicians impede clinical trial participation nationally.[17] Barriers to clinical trial participation have also been classified as structural, clinical, and attitudinal, with some differentiation according to demographic and socioeconomic factors.

Specialty-based considerations

In an era of increasing emphasis on shared

decision making, the opportunity for patients to choose to participate in a clinical trial would be of great significance.[18,19] However, several disparities exist between trials in oncology vs other medical specialties. Hirsch et al reported on the 40,970 studies registered with ClinicalTrials.gov and found that oncology trials comprise 21.8% of all trials, followed by trials focusing on mental health (9.0%), infectious disease (8.3%), diabetes mellitus (6.1%), and cardiology (5.7%).[20] Oncology studies were significantly more likely to be single-arm, open-label, and non-randomized. In addition, oncology trials were smaller compared with other specialties, with a median patient accrual of 51 vs 72 in other disease states. Early-phase trials

1 in 33
adult cancer patients
participate in clinical
trials.

Source: Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation

were also more common in oncology. Further comparisons between trials in oncology vs other medical specialties have found that oncology trials are more likely to have ongoing recruitment and are less likely to report completion of trials.[20]

Lack of awareness, commitment, and champions

Among all stakeholders—including healthcare providers, patients, advocacy groups, institutions, and third-party payers—there exists a lack of awareness about and accurate understanding of clinical trials, including the critical need for them in the community setting. Prior research focusing on efforts to diffuse and implement innovations in health services has consistently shown that three inter-related, critical factors promote behavioral change: *awareness*, *commitment*, and *champions*. [21] While awareness among community-based healthcare providers, patients, and institutions is critical in increasing clinical trial enrollment, it is largely lacking. A study evaluating the challenges and facilitators of CCOP participation found that awareness is potentially



PERSPECTIVE BY

Stephanie L. Graff, MD**Cost Barriers and Beyond**

It is time we move away from the barriers to clinical trials in the community setting. There is a large disconnect between the 85% of cancer patients treated in the community and the 3% to 5% of patients enrolled in clinical trials. Fortunately, the American Society of Clinical Oncology, Friends of Cancer Research, and the US Food and Drug Administration have been working to broaden eligibility criteria, which represent one of the most significant limitations in clinical trial accruals. Other broader issues will require collaborative solutions for increased participation and improved awareness. Outside the scope of this perspective is the unanswered question of what percentage of patients need to be treated on trial to optimize patient care and scientific advancement, without redundancy or wasted resources.

While Dr. Copur highlights the financial burden community cancer centers must endure to have a robust clinical research program, patients, too, are asked to carry a heavy financial burden. At my own Midwestern community practice, patients often drive 2 to 3 hours to receive care. The time off work, resultant job insecurity, and reduction in pay, paired with the extra gasoline expense for simple services like routine bloodwork, are no small burden. Over half of cancer patients accrue more than \$10,000 in debt, and 3% file for bankruptcy. We need to be finding ways to incorporate telehealth, decentralized labs, and mail delivery for oral drugs to help improve access for all patients, regardless of geography.

Raising awareness of clinical trials is also crucial. It is all too common for patients to believe that clinical trials are

no more than a last resort. I would love to see television and movies portray cancer patients participating in clinical trials as commonplace, or ads celebrating the patient volunteers whose clinical trial participation brought a new drug to market. Given the brisk pace of clinical research in oncology and the ability of social media to bring together physicians and patients, every trial should come paired with social media-friendly promotional materials for physicians, health systems, cooperative groups, and advocacy organizations to broadly share. This low-cost solution could increase reach and raise awareness across patients and physicians. Patient-centered language could make social media campaigns more useable than national clinical trial databases like ClinicalTrials.gov, which can be overwhelming even to experienced clinicians and advocates.

Given the adage “the best care for any patient is within a trial,” we need to broadly incorporate that message to normalize clinical trial participation. The oncology community should continue to utilize emerging technology to broadly identify patients for treatment on trial, while tearing down common barriers. I hope robust national discussion fostered in part by the Beau Biden Cancer Moonshot Initiative continues and includes the voice of valued community oncology partners in bringing the best care directly to patients.

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linked to the other two facilitators of change, commitment and champions.[21] Specifically, emphasizing and building awareness can help create new champions, while enhancing commitment to clinical trial participation.

For healthcare providers, clinical trial awareness should start in the curricula of medical schools, nursing schools, and other healthcare provider training schools, and it should extend into postgraduate schools, fellowship trainings, specialty board certifications, and maintenance of certification processes. In community settings with an active clinical trials program, good infrastructure, and widespread access to clinical trials for providers and patients, considerable variability in clinical trial enrollment rates exists between oncology providers at the same practice.[22] Values, attitudes, beliefs, training, and awareness strongly influence clinicians’ willingness to take advantage of available resources and to enroll large numbers of patients. It is possible that poor patient accrual stems from a lack of provider motivation to utilize existing resources, as well as a lack of genuine awareness of the significance of clinical trials. This may also be the case for some investigators in the academic setting. Fenton et al surveyed oncologists about their awareness of and attitudes toward clinical trials; 50% indicated that they are aware of all (7%) or most (43%) clinical trials of new agents in their geographic area. However, many oncologists noted that they are unable to closely follow the existence and findings of ongoing clinical trials due to time constraints.[23]

Awareness should also extend to patients, institutions, advocacy groups, third-party payers, and professional societies. Fifty-eight percent of Americans believe clinical trials are of great value, and an additional 38% believe they are of some value. Recently, many well-established medical centers and

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pharmaceutical industry stakeholders have adopted a direct-to-consumer advertising approach to clinical trials, mostly for those promoting a particular drug. At the same time, the lack of awareness about and promotion of the many high-quality, wide-spectrum NCI Cooperative Group clinical trials still remains. The NCI Cooperative Group and professional society websites do offer some useful information about these clinical trials. However, this web-based approach and other indirect approaches to raising awareness about clinical trials do not match the high impact of direct-to-consumer advertisements of clinical trials by industry and established medical centers.

Finally, the collaborative engagement of relevant professional medical societies in promoting community-based

As of mid-August 2018, the number of registered clinical trials worldwide was 281,000, compared with 2,119 in the year 2000.

Source: Statista.com

research may be very productive. The best example of this is ASCO's Research Community Forum (RCF), a solution-oriented venue for research sites to overcome barriers to conducting clinical trials. ASCO-RCF's key objective is to convene researchers to identify challenges in conducting research, with the intention of developing solutions and facilitating clinical trial participation, particularly in community research settings.

Conclusion

The expansion of cancer research via high-quality NCI Cooperative Group clinical trials in communities in which the majority of cancer patients live remains elusive. However, the continued efforts from the NCI, ASCO, and other stakeholders are encouraging, as is the progress made

by a number of high-performing community clinical trial sites that have found ways to improve the incredibly low rate of clinical trial participation in the community setting.^[24,25] Actualizing such an investment in community-based research will help to advance cancer research and ensure that the majority of patients with cancer have access to important advances in cancer care. ■

NOTE: This article is the first in a series of discussions in which thought leaders from various industries will share perspectives on barriers to participation in cancer clinical trials.

FINANCIAL DISCLOSURE: Dr. Copur has no financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➔ **For references visit**
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Nausea and Vomiting

Managing Side Effects From PARP Inhibitors

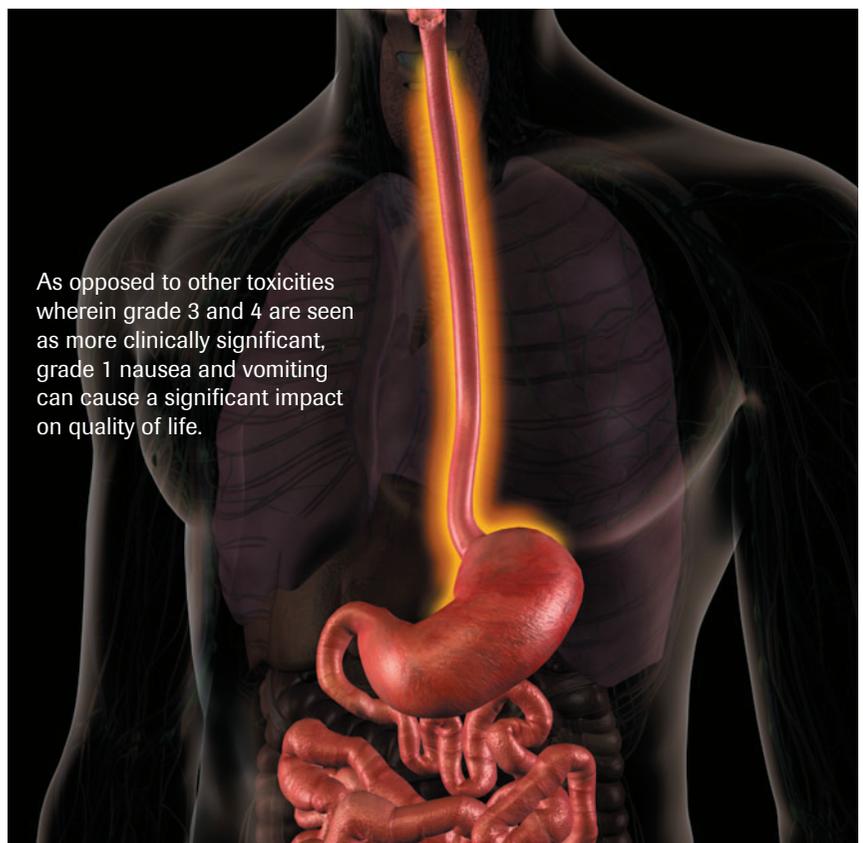
Christine C. Davis, PharmD, BCOP, and Sarah Caulfield, PharmD, BCOP

Introduction

Poly (ADP-ribose) polymerase (PARP) inhibitors are a class of oral anticancer medications that have the most evidence for use in patients with inherited germline mutations in *BRCA1/2* tumor suppressor genes. By inhibiting PARP, these agents form PARP-DNA complexes, resulting in DNA damage, apoptosis, and cancer cell death (Figure).[1]

The first US Food and Drug Administration (FDA) approval of a PARP inhibitor, olaparib, occurred in 2014; there are now four FDA-approved PARP inhibitors: olaparib, rucaparib, niraparib, and talazoparib (Table 1). Olaparib has four indications: three in ovarian, fallopian tube, and primary peritoneal cancer, and one in metastatic human epidermal growth factor receptor 2 (HER2)-negative, *BRCA*-mutated breast cancer after treatment with chemotherapy.[2] Rucaparib is indicated in ovarian, fallopian tube, and primary peritoneal cancer as a third-line treatment following chemotherapy or as maintenance treatment.[3] Niraparib is indicated only for maintenance treatment in platinum-sensitive ovarian, fallopian tube, and primary peritoneal cancer.[4] Talazoparib has one indication for treatment in locally advanced or metastatic HER2-negative, *BRCA*-mutated breast cancer.[5]

As this class of medication becomes more commonly prescribed and continues to gain new indications, it is important that providers address the most common adverse effects of these medications, which include anemia, neutro-



As opposed to other toxicities wherein grade 3 and 4 are seen as more clinically significant, grade 1 nausea and vomiting can cause a significant impact on quality of life.

penia, gastrointestinal (GI) toxicity, and fatigue. When prescribing oral agents with known risk of GI toxicity, providers must proactively prescribe medications to prevent these toxicities, such as nausea and vomiting, in order for the patient to remain adherent to the prescribed dose without significant decline in quality of life.[6] We will outline here how to prevent and treat nausea and vomiting among patients being treated with PARP inhibitors.

PARP Inhibitor–Associated GI Toxicity

In the 2014 Kaufman trial, as well as the SOLO-1 and SOLO-2 trials, nausea was the most commonly reported adverse event seen with olaparib treatment (all grades, 62%–77%; grade ≥ 3 , 1%–6%), with a lower incidence of vomiting (all grades, 35%–40%; grade ≥ 3 , 1%–3%).[7-9] In the ARIEL2 and ARIEL3 trials, nausea was also the most common adverse event in the rucapar-

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ib group (all grades, 75%; grade ≥ 3 , 4%); vomiting was also less common (all grades, 37%–42%; grade ≥ 3 , 2%–4%).[10,11] Similarly, the NOVA trial showed that the most common adverse effect with niraparib was nausea (all grades, 74%; grade ≥ 3 , 3%), with vomiting of all grades occurring in 34% of patients (grade ≥ 3 , 2%). [12] However, nausea and vomiting were less prevalent with talazoparib in the EMBRACA trial (for nausea: all grades, 49%, grade ≥ 3 , < 1%; for vomiting: all grades, 24%, grade ≥ 3 , 2%).[13]

As opposed to other toxicities wherein grade 3 and 4 are seen as more clinically significant, grade 1 nausea and vomiting can cause a significant impact on quality of life. The National Comprehensive Cancer Network (NCCN) guidelines for antiemesis categorize the emetogenic potential of oral anticancer agents based on the frequency of vomiting/emesis reported (Table 2). Treatments are considered to have a moderate to high frequency if emesis occurs in $\geq 30\%$ of patients, which places olaparib, niraparib, and rucaparib in this category. However, talazoparib would be considered to have minimal to low emetic risk.[14]

Management of Nausea and Vomiting

When assessing a patient's risk for chemotherapy-induced nausea and vomiting (CINV), it is important to consider not only the emetic risk of the therapeutic agent, but also to take into account the individual patient's risk factors. Women, younger patients, patients with lower alcohol intake history, and those with a history of motion sickness are

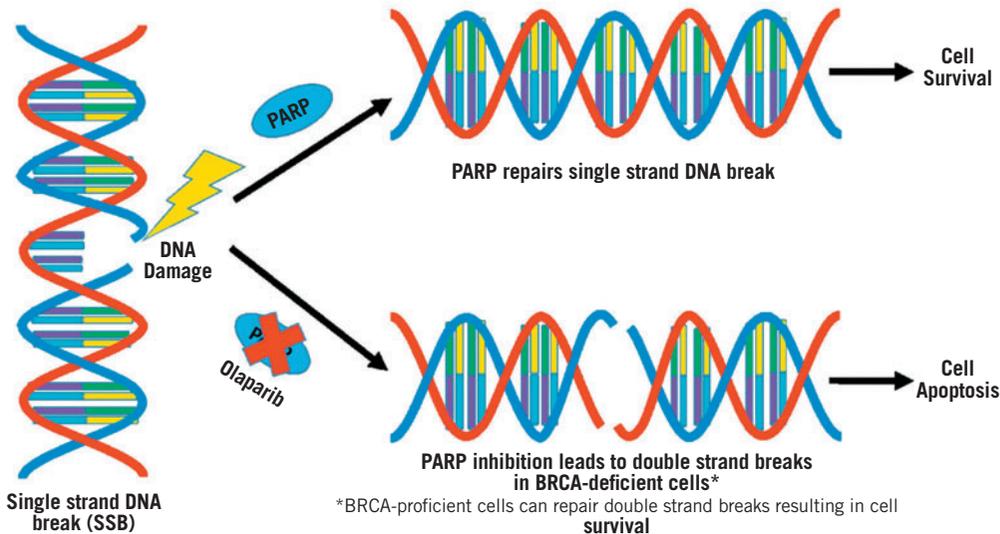


FIGURE Illustration of Olaparib Mechanism Specifically in BRCA-Deficient Cells Compared With Normal Cells[1]

PARP = poly (ADP-ribose) polymerase.

Nausea and vomiting induced by systemic or radiation therapy can significantly affect a patient's quality of life, leading to poor compliance with further treatment.

-Source: J Natl Compr Canc Netw. 2017;15:883-93.

at increased risk of experiencing CINV during treatment.[14,15] For oral cancer agents that fall in the moderate to high emetic risk category (including olaparib, rucaparib, and niraparib), the NCCN recommends that the patient take a serotonin (5-HT₃) receptor antagonist, such as ondansetron 8 to 16 mg daily, ideally approximately 30 minutes before a PARP inhibitor dose.[14] All four of the PARP inhibitors currently approved can be taken with or without food; therefore, the patient should be counseled to take the medication after a meal if they experienced nausea taking it on an empty stomach.[2-5] Of note, olaparib and rucaparib are both dosed twice daily and may require the anti-nausea medication to also be taken

twice per day.[2,3] Niraparib is taken only once daily and is recommended to be taken at night to help prevent CINV. [4] Compliance to antiemetic therapy should be encouraged when initiating new PARP inhibitor therapy to avoid drug intolerance and potential for unnecessary interruption in therapy. At each clinic visit, nausea and vomiting should be assessed to determine if any adjustments need to be made to the antiemetic regimen.

For patients who experience CINV during treatment, it should first be determined if they are compliant with their antiemetic regimen, refractory to the antiemetic therapy (experiencing CINV with the majority of doses), or experiencing breakthrough nausea

TABLE 1 Indications of FDA-Approved PARP Inhibitors[2-5]

Pharmacologic Agent	Indication(s)
Niraparib	Maintenance treatment in platinum-sensitive ovarian cancer, fallopian tube cancer, and primary peritoneal cancer
Olaparib	Ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and metastatic HER2-negative, <i>BRCA</i> -mutated breast cancer after treatment with chemotherapy
Rucaparib	Ovarian, fallopian tube, and primary peritoneal cancer as a third-line treatment following chemotherapy or as maintenance treatment
Talazoparib	Locally advanced or metastatic HER2-negative, <i>BRCA</i> -mutated breast cancer

FDA = US Food and Drug Administration; PARP = poly (ADP-ribose) polymerase; HER2 = human epidermal growth factor receptor 2.

TABLE 2 National Comprehensive Cancer Network Categorization of Emetic Potential for Intravenous Agents[14]

Risk Category	Incidence of Acute Emesis
High emetic risk	> 90% of patients
Moderate emetic risk	> 30% to 90% of patients
Low emetic risk	10% to 30% of patients
Minimal emetic risk	< 10% of patients

with only occasional episodes. If first-line prevention with a 5-HT₃ receptor antagonist is not sufficient, the patient should try alternative treatments for CINV. The general recommendation for patients who are refractory to initial therapy is to stop the first-line agent and switch to a drug with a different mechanism. For patients who experience only breakthrough CINV, it is recommended to add one agent from a different drug class to the current regimen.

The NCCN also recommends olanzapine, lorazepam, dronabinol, haloperidol, metoclopramide, scopolamine transdermal patch, prochlorperazine or promethazine, an alternative 5-HT₃ receptor antagonist such as dolasetron or granisetron, or a steroid such as dexamethasone for the prevention of CINV. When deciding between these options, one should consider patient-

and drug-specific factors. For example, olanzapine should be started with a low dose and it is recommended that it should be taken at night, since it can cause significant drowsiness. Age should be considered when using benzodiazepines such as lorazepam, since they can cause more complications in elderly patients, though they may be helpful if the patient is experiencing anticipatory nausea. Dronabinol may be useful if the patient is also experiencing decreased appetite. The scopolamine patch may help if the patient finds that they are more sensitive to motion sickness while on PARP inhibitor therapy. Granisetron is also avail-

able as a patch if the patient is vomiting and unable to keep down oral medications. Dexamethasone should be recommended with caution, since there are notable complications with long-term use of steroids and it may need to be used daily with PARP inhibitor-related nausea. If a patient vomits after a medication dose, it is important to counsel them to not take another dose until the next scheduled dose. For patients who continue to experience CINV after attempted antiemetic optimization and have compromised quality of life, dose reduction may be required (Table 3).

Additional Considerations With PARP Inhibitors

Drug interactions should be taken into account when choosing which PARP inhibitor to prescribe. For example, a dose reduction for olaparib would be required if given with cytochrome P450 3A4 (CYP3A4) inhibitors.[2] Aprepitant or fosaprepitant, netupitant, and fosnetupitant should all be avoided in patients on olaparib treatment, since they have interactions with medications metabolized through CYP3A4. Patients should also be counseled to avoid grapefruit juice and Seville oranges when taking olaparib.[2] For patients on talazoparib, a dose reduction is required when given with P-glycoprotein inhibitors.[5]

Additionally, mild increases (grade 1 or 2) in serum creatinine are possible due to transporter inhibition with olaparib and rucaparib. Continuation of therapy during evaluation is recommended to rule out true renal dysfunction. [6] Mild increases in transaminases (aspartate and alanine transaminases) may be seen within the first 28 days of rucaparib treatment. Providers should note that they do

IN PRACTICE

If first-line prevention of CINV with a 5-HT₃ receptor antagonist is not sufficient, the patient should try alternative treatments.

not need to hold the medication unless transaminases exceed 5 times the upper limit of normal (ULN) or more than 3 times the ULN for bilirubin and more than 2 times the ULN for alkaline phosphatase.[6] Lastly, additional GI adverse effects that should be monitored with PARP inhibitor use include constipation, diarrhea, abdominal pain, dyspepsia, dysgeusia, and decreased appetite.[2-5]

Conclusion

Providers should be aware of the potential risk for GI toxicity with PARP inhibitors. Patients initiating olaparib, rucaparib, or niraparib should receive prophylactic antiemetic medication to help prevent nausea and vomiting throughout the treatment course. Patients should be monitored for compliance and efficacy of antiemetic therapy to help preserve quality of life and prevent inappropriate dose reduction. There are several different classes of medication available for use as antiemetic therapy if initial therapy is not

TABLE 3 PARP Inhibitors Dose Reduction Recommendations for Toxicity

Drug	Dose Reduction
Olaparib (tablets)[2]	Starting dose: 300 mg twice daily First dose reduction: 250 mg twice daily Further reduction: 200 mg twice daily
Rucaparib[3]	Starting dose: 600 mg twice daily First dose reduction: 500 mg twice daily Second dose reduction: 400 mg twice daily Third dose reduction: 300 mg twice daily
Niraparib[4]	Starting dose: 300 mg once daily First dose reduction: 200 mg once daily Second dose reduction: 100 mg once daily *If further dose reduction below 100 mg daily is needed, discontinue niraparib.
Talazoparib[5]	Starting dose: 1 mg once daily First dose reduction: 0.75 mg once daily Second dose reduction: 0.5 mg once daily Third dose reduction: 0.25 mg once daily

sufficient or is contraindicated. Each patient is different and will require continued monitoring and potential alteration in antiemetic therapy to help them remain compliant and maintain a good quality of life. ■

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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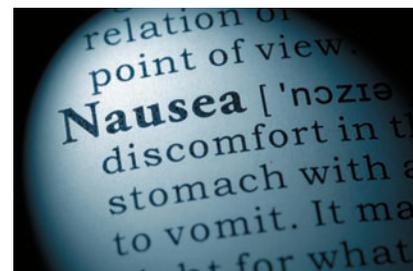
Vist our site for more research and perspectives on cancer-linked side effects.



Managing Nausea and Vomiting in Patients With Cancer: What Works
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Study Casts Doubt on Antiemetic Value of Ginger Supplement in Cisplatin Chemotherapy
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Poor Adherence to Guidelines for Preventing Chemotherapy-Induced Nausea, Vomiting
cancernetwork.com/CINV-guideline-adherence

Antidepressants in Patients With Advanced Cancer: When They're Warranted and How to Choose Therapy

Ebtesam Ahmed, PharmD, MS

ABSTRACT: Cancer patients with depression experience more physical symptoms, pain, and fatigue; have a poorer quality of life; and are more likely to encounter negative thoughts compared with cancer patients who are not depressed. Accurate assessment and treatment of depression can have a positive impact on improving a patient's quality of life. Pharmacotherapy for depression in patients with advanced cancer should be guided by a focus on symptom reduction, irrespective of whether the patient meets the diagnostic criteria for major depression. For effective treatment of a depressive illness, antidepressant medication and cognitive behavioral therapy need to be initiated sooner rather than later to reduce symptom burden and improve quality of life.

PERSPECTIVE

Mirat Shah, MD, Kerry O'Connor, MD, and Thomas J. Smith, MD, FACP, discuss screening for depression on page 64.

Introduction

Depression is the most common psychological condition in patients with cancer. To improve the rate of recovery among such individuals, it is important that clinicians learn to recognize and treat the symptoms associated with this condition. Several practice guidelines recommend screening every patient with cancer for depression. In terms of treatment, both psychotherapy and pharmacotherapy have been shown to be effective in treating depression in this population. When pharmacotherapy is warranted, selection of treatment agent(s) should be made based on the patient's medical history, cancer type, and disease severity. Increased awareness about the risk of depression along with knowledge of how to identify symptoms and initiate treatment are essential to improve the overall quality of life for patients with cancer.

Prevalence

The reported prevalence of depression in patients with cancer varies from 3% to 38%.^[1] Depressive symptoms in this population range from feelings of sadness



to a clinical diagnosis of major depressive disorder (MDD). The rate of depression is highest in those closest to the end of life and in patients with certain types of cancer, including pancreatic cancer, lung cancer, gastric cancer, and oropharyngeal cancer. [2] MDD is present in 16% of individuals with cancer, while minor depression and dysthymia occur in about 22% of patients. This wide variability can be explained by the lack of consensus regarding the appropriate diagnostic criteria to utilize in the setting of advanced illness, as well as by the differences in various assessment methods.[3]

Burden of Depression

Psychological distress is a major cause of concern among patients with advanced cancer.[4] Depressive syndromes are highly correlated with a reduced quality of life, increased difficulty managing the course of disease, decreased adherence to treatment, and earlier admission to inpatient or hospice care.[5] A meta-analysis revealed that minor or major depression increases the rate of mortality by up to 39%; in addition, patients displaying even a few depressive symptoms may be at a 25% increased risk of mortality.[6] Depression weakens the patient's ability to experience pleasure, sense, and connection; it also intensifies pain and other symptoms and causes suffering and worry in friends and family members.

IN PRACTICE

Every patient with cancer should be screened for depression during the initial visit to the oncologist.

Screening and Diagnosis

Depression is underdiagnosed in patients with cancer due to the overlap in symptoms caused by these conditions, such as fatigue, insomnia, and anorexia.[1] The National Comprehensive Cancer Network (NCCN) provides the Guidelines for Distress Management, which are intended for any psychosocial problems found in patients with cancer. These guidelines recommend that every cancer patient be

TABLE 1 Risk Factors for Depression[8-10]

<ul style="list-style-type: none"> ▪ Age and gender <ul style="list-style-type: none"> ▪ Young age ▪ Women > men
<ul style="list-style-type: none"> ▪ Prior history of depression
<ul style="list-style-type: none"> ▪ Uncontrolled symptoms <ul style="list-style-type: none"> ▪ Uncontrolled pain can decrease the patient's quality of life and increase the burden of disease, which can lead to depression
<ul style="list-style-type: none"> ▪ Type of illness
<ul style="list-style-type: none"> ▪ Existential concerns and spirituality
<ul style="list-style-type: none"> ▪ Poor social support
<ul style="list-style-type: none"> ▪ Functional status
<ul style="list-style-type: none"> ▪ Disease progression

screened for depression during his or her initial visit to the oncologist. A screening tool called the "Distress Thermometer," also available from the NCCN, can aid in this process. The tool asks patients to rank their level of stress during the past week on a scale of 0–10. A score of 4 or higher indicates that the patient should be referred to mental health services.[7]

Clinicians often rely more on the psychological or cognitive symptoms of depression (ie, worthlessness, hopelessness, excessive guilt, and suicidal ideation) than the physical/somatic signs (ie, weight loss, sleep disturbance) when making a diagnosis of MDD in patients with advanced disease. To effectively treat patients' depression, it is also important that clinicians be able to recognize the risk factors that can lead to depression (see Table 1 for a complete list).[8-10]

In addition to recognizing risk factors for depression, it is important that clinicians be able to monitor patients for an appropriate reaction to advanced disease and death. If any depressive syndrome is suspected, physicians should utilize appropriate screening tools to aid in the

diagnosis. The Patient Health Questionnaire-2 (PHQ-2), a two-item depression screener, can be utilized among patients who screened positive for depression in order to diagnose the condition.[11] Self-report tools, such as the 21-item Beck Depression Inventory (BDI) or the visual analog scale, may be helpful if a direct face-to-face evaluation is not feasible.[12] However, it should be noted that, compared with a brief interview addressing the commonly accepted disease criteria, the efficacy of these tools as a diagnostic aid is inferior.

Guidelines and self-report tools for depression

The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) is one of the most common tools used to diagnose depression, particularly among non-terminally ill patients.[14] The DSM-5 outlines somatic complaints associated with the condition, such as changes in weight or appetite, sleep disturbance, fatigue or loss of energy, and difficulty thinking or concentrating. MDD is often not recognized in patients with cancer because the somatic symptoms of depression—including changes in appetite, energy, and/or sleep—may be attributed to normal cancer-related changes or to cancer treatment side effects. In addition, these somatic symptoms may overlap with the changes seen in patients

with cancer who are not depressed.[14] This is why, in addition to the self-reported tools discussed previously, it is very important that physicians assess patients for signs of depression. This can be done by conducting an interview with the patient. Self-report tools may not provide accurate enough evidence on their own to diagnose depression. Clinicians must also ascertain that the patient's symptoms are causing functional impairment.

Treatment

In cancer patients, the treatment of depression should be individualized to address the patient's depressive symptoms, as well as the disease-related and psychosocial

factors contributing to the development of depression. Typically, antidepressant medication is most effective for severe depression, whereas psychotherapy is recommended for both mild and severe cases of depression.[15,16] Cognitive behavioral therapy (CBT) is the most commonly recommended psychotherapy; compared with other types of therapy, the most evidence from clinical trials involving patients with major depression is available for CBT.[17] The NCCN guidelines also recommend supportive psychotherapy.[7] Among patients recently diagnosed with cancer, CBT, relaxation strategies, and problem-solving approaches are recommended.

One specific type of supportive ther-

apy, dignity therapy, has been shown to improve depressive symptoms in clinical trials.[18] Dignity therapy is an individualized type of psychotherapy that provides patients the opportunity to discuss their preferences, such as reflecting on what matters most to them or on how they would like to be remembered by their loved ones. Patients receive an edited transcript of the session to share with friends and family.[19] Lastly, the NCCN guidelines recommend that cancer patients complete family and couples therapy to lessen distress. Studies have shown that both of these types of therapy are associated with reduced distress and grief among families.[20]

PERSPECTIVE BY

Mirat Shah, MD, Kerry O'Connor, MD, and Thomas J. Smith, MD, FACP

Asking Matters Most: Depression in Advanced Cancer



Depression is common in patients with advanced cancer and leads to poor symptom control and decreased life expectancy, as highlighted in this article. Ms. Ahmed notes that depression is underdiagnosed in this group because some symptoms—loss of appetite, fatigue, and trouble sleeping—mimic the symptoms of advanced cancer. In our experience, there are additional factors that prevent diagnosis.

Oncology providers tend to think that depression is a normal reaction to advanced cancer, rather than something that can be treated. They may feel ill-equipped to manage depression once it is diagnosed, or that a different member of the care team is better-suited to the task. In addition, clinicians are pressed for time during clinic visits. Without a prompt, patients often don't bring up these symptoms

and instead try to cope on their own.

Asking the simple question "Are you depressed?" helps patients feel heard and valued, and has acceptable sensitivity and specificity for cancer patients.[1] After we asked this question of a 35-year-old woman with advanced uterine cancer at our clinic, she remarked, "Thank you for listening. No one ever listens. Listening helps." Another man with metastatic colorectal cancer who was asked this same question remarked, "Thank you for being human." These responses highlight that being present and actively listening to patients are therapeutic acts in and of themselves.

After asking the question, additional members of the care team can assist as needed, and, as noted in this article, therapy and medication may also help. But asking is the most important step. Although we sometimes may not

be able to cure, by asking and listening, we can still heal.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit
cancernetwork.com/cancer-depression

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TABLE 2 Characteristics of the Available Agents to Treat Depression[50-67]

Drug	Initial Dose	Dose Range	Side Effects	Notes
Psychostimulants				
Methylphenidate IR	2.5 mg PO q morning and noon	5-10 mg PO q morning and noon	Insomnia (if given 6-8 h before bedtime), restlessness, agitation, palpitations, increased BP, anorexia, weight loss, tremor, dry mouth	For older patients, start at low dose and titrate slowly Low dose can stimulate appetite, relieve fatigue and weakness, and promote sense of well-being
Dextroamphetamine	5 mg q morning	5-15 mg PO q morning and noon	Abdominal pain, loss of appetite, headache, insomnia, tremor, dysphoric mood, anxiety, euphoria, restlessness, weight loss	Start at a low dose and taper slowly Can cause significant cardiovascular changes (BP, HR)
Modafinil	100 mg q morning	200 mg PO q morning	Headache, nervousness, dizziness, insomnia, weight loss, decreased appetite, nausea, diarrhea, hypertension, palpitations, tachycardia	Start at a low dose and taper slowly Must have cardiovascular assessment prior to initiating therapy
Selective Serotonin Reuptake Inhibitors				
Citalopram	10-20 mg QD	20-40 mg QD	Dose related: jitteriness, restlessness, anxiety, agitation, headache, diarrhea, weight gain, nausea, sexual dysfunction Risk of QTc prolongation	Headache and jitteriness will subside within 4-7 d Dose must be tapered when discontinuing an SSRI, except for fluoxetine due to its long half-life
Escitalopram	10 mg QD	10-20 mg QD	Headache, nausea, anxiety, restlessness, sexual dysfunction	Clinical response is delayed Must taper off slowly when discontinuing therapy
Sertraline	50 mg QD	50-200 mg QD	Increased GI risk (diarrhea), insomnia, agitation	Better tolerated by severely ill patients due to little metabolite accumulation
Fluoxetine	10 mg QD	20-60 mg QD	Insomnia, agitation	Full response may not be seen until 8-12 wk after initiation of therapy Less well tolerated compared with sertraline
Paroxetine	20 mg QHS	20-40 mg QD	Increased risk of sedation, highest sexual dysfunction incidence among all SSRIs, weight gain, orthostatic hypotension	Better tolerated by severely ill patients due to little metabolite accumulation Rapid withdrawal syndrome
Serotonin-Norepinephrine Reuptake Inhibitors				
Venlafaxine ER	37.5 mg QD	75-225 mg QD	Moderate sexual dysfunction, low GI toxicity, slight insomnia, weight gain, QTc prolongation Dose-dependent increase in BP and HR	Severe withdrawal symptoms if not tapered
Desvenlafaxine	50 mg QD	50-100 mg QD	Chest pain, seizures, hallucinations, constipation	Shorter half-life
Duloxetine	40 mg QD	40-60 mg QD	Slight insomnia, weight gain, sexual dysfunction Low GI toxicity	High number of drug interactions Avoid if creatinine clearance < 30 mL/min
Atypical Antidepressants				
Bupropion	100 mg Q morning initially, then BID	150 mg Q morning and mid-afternoon (BID)	Insomnia, tremor, slight QTc prolongation, GI toxicity (constipation) Dose-dependent increase in BP	Avoid in patients with seizure disorders or depression with agitation
Mirtazapine	15 mg QHS	15-45 mg QHS	High risk of drowsiness, weight gain, sedation, dry mouth Slight sexual dysfunction, QTc prolongation	Risk of accumulation with renal and/or hepatic insufficiency
Tricyclic Antidepressants				
Amitriptyline	25-50 mg HS	100-300 mg in divided doses	Unilateral weakness, abnormal HR, unusually bruising, sedation, orthostatic hypotension, tachycardia	Not well tolerated in the older palliative care patients due to anticholinergic effects
Doxepin	25-50 mg HS or in divided doses	100-300 mg QD	Rapid HR, trouble urinating, yellowing of the eyes and skin	
Desipramine	25-50 mg q morning	100-200 mg q morning, or in two divided doses	Anticholinergic effects, arrhythmia, orthostatic hypotension	Not well tolerated in older palliative care patients due to anticholinergic effects
Imipramine	25-50 mg HS or divided doses	100-300 mg daily	Hallucinations, insomnia, bad dreams, yellowing of the eyes and skin	Not well tolerated in the older palliative care patients due to anticholinergic effects

Continued on page 66

Continued from page 65

Drug	Initial Dose	Dose Range	Side Effects	Notes
Nortriptyline	25 mg QHS	50–150 mg QHS, or in two divided doses	Anticholinergic effects, drowsiness, orthostatic hypotension, weight gain, cardiac arrhythmia, agitation	Usually avoided due to anticholinergic effects
Monoamine Oxidase Inhibitors				
Tranlycypromine	10 mg PO QD	30–60 mg PO QD	High sexual dysfunction; low insomnia/agitation and orthostatic hypotension; slight anticholinergic effects, weight gain, GI toxicity	Interaction with sympathomimetic leads to hypertensive crisis, and serotonergic medications lead to serotonin syndrome
Phenelzine	15 mg on d 1, increased to 15 mg TID over 2–3 d, as tolerated	60–90 mg PO QD	Anticholinergic effects, sedation, orthostatic hypotension	
Selegiline	6 mg/24 h transdermal	Up to 12 mg/24 h; dose increase in increments of 3 mg/24 h	Low anticholinergic effects, insomnia, agitation, orthostatic hypotension	Dietary restrictions required if 9 mg/24 h or 12 mg/24 h are used
Serotonin Modulators				
Nefazodone	100 mg PO BID	150–600 mg/d in 2 divided doses	Low GI risk, drowsiness, hepatotoxicity	Administer with food to reduce nausea Monitor liver function
Trazodone	50 mg taken 30–60 min before QHS	200–400 mg taken 30–60 min before bedtime for hypnotic effect	High drowsiness, moderate orthostatic hypotension and GI toxicity, low weight gain and sexual dysfunction	Adjunct modality with an SSRI for treatment of insomnia

BP = blood pressure; ER = extended-release; GI = gastrointestinal; HR = heart rate; IR = immediate-release; SSRI = selective serotonin reuptake inhibitor.

Pharmacotherapy selection. Several classes of antidepressants are available to treat depression, including:

- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs) and tetracyclic antidepressants
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Serotonin modulators (eg, trazodone)
- Atypical antidepressants (eg, mirtazapine)

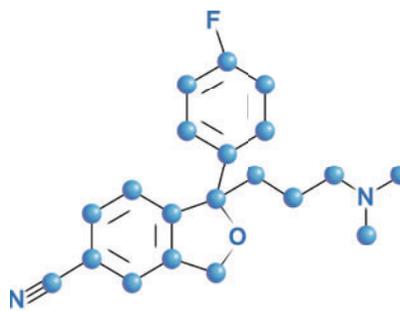
When selecting an antidepressant, clinicians should consider the patient’s symptoms and concurrent medications. Characteristics of the available agents to treat depression are described in **Table 2**.

Choice of Pharmacotherapy

When it comes to selecting pharmacotherapy to treat depression in patients with cancer, no particular medication class has been proven to be superior in terms of efficacy. Thus, when choosing a medication to initiate treatment, physicians must consider a number of factors. First and foremost, an assessment of the patient’s symptoms should be completed, since certain medications may be more beneficial in treating specific ailments. For example, a patient with symp-

toms of both depression and insomnia may benefit from an antidepressant that has a more sedative effect. Clinicians should also inquire whether the patient has ever used antidepressant medications in the past and, if so, whether they were effective.

Other considerations when selecting pharmacotherapy for depression include potential drug-drug interactions and adverse side effects. Cost issues, as well as the patient’s comorbid symptoms—such as insomnia, neuropathic pain, or poor appetite—should be considered. Furthermore, due to inadequate studies among the cancer patient population, dosing of antidepressants must be highly individualized. Failure to adhere to antidepressant therapy leads to several high-risk outcomes,[21] particularly among those who are nonadherent during the first 6 weeks of therapy.[22] Individuals who adhere to antidepressant therapy early and continue to take their medication as prescribed are more likely to recover from depression



Citalopram

The first-line therapy for depression is an SSRI, namely citalopram or escitalopram.

and to avoid future relapse.

SSRIs

The preferred first-line therapy for depression is an SSRI, the most commonly prescribed class of antidepressants. The favorable efficacy and side effect profiles associated with SSRIs make these agents the most attractive for

some patients with cancer who are diagnosed with depression. SSRIs are generally as effective as TCAs for the treatment of depression, and they have a wider margin of safety than TCAs in the event of an overdose.[23] Compared with TCAs, SSRIs are associated with fewer cardiac arrhythmias, hypotension, and anticholinergic effects.[24] In addition, SSRIs generally have reduced sedative and autonomic properties. SSRIs should be started at a low dose and then titrated to the minimum effective dose to reduce the potential for side effects, such as jitteriness, restlessness, anxiety, agitation, headache, sexual dysfunction, gastrointestinal symptoms (ie, diarrhea and nausea), and insomnia.[23]

Among the SSRIs, citalopram or escitalopram are considered to be first-line therapy because they are well tolerated and pose few drug-drug interactions. Furthermore, since these agents do not significantly inhibit cytochrome P450 (CYP450) 2D6 (CYP2D6), they can be used in patients taking tamoxifen.

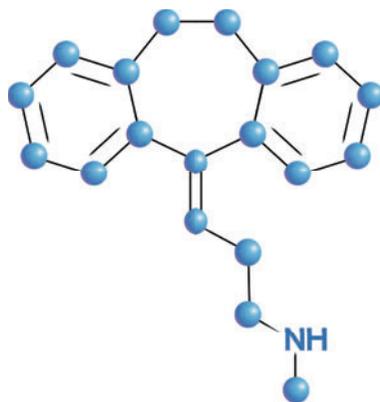
In a study evaluating the use of escitalopram among cancer patients in palliative care, 18

patients who met the DSM-IV criteria for depressive disorder were treated with 10 mg for 2 weeks. Patients were evaluated using the Hospital Anxiety and Depression Scale (HADS) and the Mini-Mental Adjustment to Cancer Scale (Mini-MAC). At the endpoint, there was a significant reduction in anxiety, as measured by HADS, and in hopelessness-helpllessness, as measured by Mini-MAC.[25]

Fluoxetine has limited clinical use in advanced illnesses due to its long half-life, since it takes 5 to 6 weeks to reach steady-state drug concentrations; in addition, its potential for significant drug-drug interactions is high because it inhibits hepatic drug-metabolizing enzymes, such as CYP450.[26,27] Paroxetine can be sedating and may lead to withdrawal phenomena with missed doses.[28] Sertraline has been shown to reduce fatigue, appetite, anhedonia, and suicidal thoughts in all types of depression in patients with cancer undergoing chemotherapy.[29] In older adults with advanced cancer, the initial SSRI dose should be reduced to approximately one-half that used in healthy patients.

TCA

An older class of antidepressants, TCAs have demonstrated efficacy in depressed,



Nortriptyline

TCAs such as nortriptyline are not as well tolerated as other antidepressants due to their anticholinergic properties.

constipation. Older adults are particularly susceptible to confusion and hallucinations. TCAs may also induce delirium and prolong the QTc interval, and they can be dangerous in the event of overdose. [32] Therefore, their use is limited, since they may be problematic for patients with cardiac conditions and those taking other medications with anticholinergic properties. Of note, nortriptyline and desipramine have reduced anticholinergic properties compared with other tricyclics.

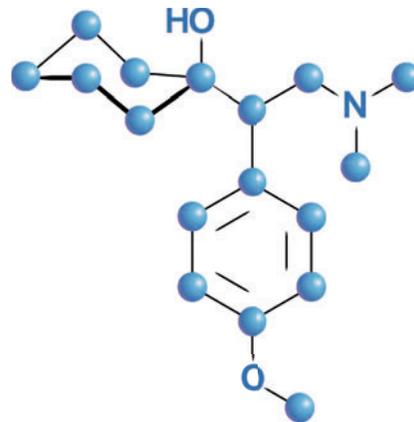
SNRIs

SNRIs are another class of antidepressants that may be helpful for patients with cancer. Research has shown that SNRIs are beneficial in managing neuropathic pain, vasomotor instability, or anxiety-predominant depression.[33] Venlafaxine is one example of an SNRI that is well tolerated in cancer patients. It is not significantly active in the CYP450 system, and, compared with other antidepressants, it is somewhat less protein-bound.[34] Venlafaxine is considered to be the first-line therapy in the SNRI class for those receiving tamoxifen due to its lack of CYP2D6 inhibition, as well as its ability to reduce hot flashes in those receiving chemotherapy or experiencing menopause as a result of taking tamoxifen. However, it

medically ill patients. [30] TCAs are also proven adjuvant analgesics for neuropathic and chronic low back pain.[31] While TCAs have been used frequently in the cancer setting, they are not as well tolerated as other antidepressants. This is due to their anticholinergic properties, which may cause symptoms such as dry mouth, blurred vision, urinary retention, and

should be used with caution in those with hypertension, as high doses of this agent may elevate blood pressure.

Duloxetine is another SNRI that is approved to treat anxiety, diabetic neuropathy, and chronic musculoskeletal pain. [35] A prospective, 12-week, case-control study compared the use of duloxetine in patients with depression and cancer vs depression alone. Patients received an initial dose of duloxetine 30 mg, which was then titrated to 60 mg after 1 week and up to 120 mg after 1 month, based on response. Patients were assessed using HADS, the Clinical Global Impression Scale-Severity (CGI-S), and the Montgomery-Åsberg Depression Rating Scale (MADRS). In individuals with both cancer and depression, scores significantly improved on each of the depression scales at both 4 and 12 weeks.[36] Du-



Venlafaxine

Venlafaxine is one example of an SNRI that is well tolerated in cancer patients.

looxetine is contraindicated in patients with heavy alcohol use or chronic liver disease. Milnacipran has been shown to be significantly effective in the treatment of depression and fibromyalgia.[37,38]

Other antidepressants

The antidepressant bupropion has been shown to decrease fatigue and improve depression symptoms in cancer patients. An open-label study examined sustained-release bupropion for depres-

sion and fatigue in the cancer population. Patients took bupropion for 4 weeks after titrating to 300 mg or the maximum tolerable dose. Nine of the patients were identified as depressed at baseline, based on a Hamilton Depression Rating Scale (HAM-D) score of > 17. Both depressed and non-depressed patients had significantly lower HAM-D scores at the endpoint, with depressed patients showing a greater decrease in HAM-D scores compared with non-depressed patients.[39] Bupropion is contraindicated for cancer patients with central nervous system disorders due to its association with increased prevalence of seizures.[40]

While trazodone is an effective antidepressant, its use is limited because it causes significant sedation.[41] However, it may be helpful among patients with sleep disturbances, as well as for those who require an adjunct analgesic effect in addition to an antidepressant effect. Nefazodone, another antidepressant, is associated with liver failure and has been withdrawn in many countries; therefore, it should not be used in medically ill patients.[42]

Although mirtazapine has a sedative effect, it has been shown to be effective for improving pain symptoms, as well as depression and quality of life in patients with advanced cancer.[43] When used at low doses, mirtazapine has also been shown to improve appetite and insomnia, particularly among patients on the 15 mg/day dose, and to provide sedation when warranted.[44]

Monoamine oxidase inhibitors (MAOIs) are generally considered to be less desirable for treating depression in patients with advanced medical illnesses due to the substantial number of adverse interactions associated with these agents. MAOIs are generally reserved for patients who have shown a past preferential response to them for depression.[45]

Psychostimulants

Antidepressants may not have sufficient time to reach their full effect in patients with a prognosis of days or weeks. In

Summary Recommendations

- For patients with neuropathic pain and depression, consider duloxetine or venlafaxine.
- If the patient has insomnia or anorexia, consider the use of mirtazapine.
- When polypharmacy is present, consider citalopram, escitalopram, or mirtazapine.
- Closely monitor patients initiated on an antidepressant for adverse effects and the potential need for dose titration.
- Refer to social work and/or spiritual support services if the depression appears to be escalating in relation to social or spiritual factors.
- For depressed patients with a limited prognosis, consider the use of a psychostimulant such as methylphenidate.

these cases, psychostimulants may be beneficial. Compared with antidepressants, psychostimulants have a more rapid onset of action of within 24 to 48 hours. They have been shown to improve attention, concentration, and overall performance on neurologic testing in the medically ill.[46] In addition, they can improve mood, appetite, and sense of well-being. Although generally well-tolerated, psychostimulants may cause side effects such as agitation, nausea, anorexia, insomnia (particularly if administered within 6 to 8 hours of bedtime), anxiety, and tremor. Modafinil has fewer sympathomimetic effects than amphetamines and is often a good choice for older patients.[47] Psychostimulants should be avoided in patients with delirium and used with caution in those with heart disease. Although the data on

psychostimulants are somewhat mixed, controlled trials have shown their benefit as a monotherapy or to augment the effects of another antidepressant.[47]

Ketamine

A number of case reports and one small placebo-controlled trial of intravenous ketamine have shown that ketamine can rapidly improve depressive symptoms in patients with refractory depression in the setting of a terminal illness, particularly in the setting of chronic pain.[48,49]

Conclusion

Depression is underdiagnosed and undertreated in chronically ill cancer patients. It is imperative that healthcare providers be proactive in screening for depression, as well as in educating patients about the available treatment options for depression. Each individual case of depression is different and must be treated according to the patient's medical history, cancer prognosis, and severity of symptoms. When selecting therapy, physicians must evaluate the side effect profile of each agent to ensure it is appropriate for the patient. A specific patient interview should also be conducted in order to carefully confirm the diagnosis and to avoid confusing the symptoms of progressing cancer with those of major depression. Once pharmacotherapy is initiated, close monitoring for adverse effects and the potential need for dose titration is warranted. ■

FINANCIAL DISCLOSURE: Ms. Ahmed has no financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➤ For references visit cancernetwork.com/cancer-depression



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Incidental Primary Squamous Cell Carcinoma of the Kidney Within a Calyceal Diverticulum Associated With Nephrolithiasis

Austin Lunney, BS, Irfan Warraich, MD,
and Pranav Sharma, MD

THE CASE

A 64-year-old Hispanic man was referred to the urology clinic by his primary care physician for evaluation of right upper pole kidney stones associated with recurrent urinary tract infections (UTIs; **Figure 1**). The patient's medical history was significant for well-controlled hypertension, type 2 diabetes mellitus, hyperlipidemia, and epilepsy, as well as a remote history of nephrolithiasis. In the past, he underwent several surgeries, including laparoscopic cholecystectomy, bilateral inguinal hernia repairs with mesh, and a percutaneous nephrolithotomy for a complete right staghorn renal calculus over 10 years ago, the latter of which was complicated by a pneumothorax requiring chest tube placement. The patient denied any workup or prophylaxis for stone formation. He denied any history of tobacco, alcohol, or substance abuse.

On evaluation, the patient had normal baseline renal function, with a serum creatinine level of 1.0 mg/dL. Follow-up urine cultures revealed recurrent, pan-sensitive *Klebsiella pneumoniae* UTIs. The patient denied any urinary complaints, and a physical examination was largely unremarkable. A follow-up CT urogram of the abdomen and

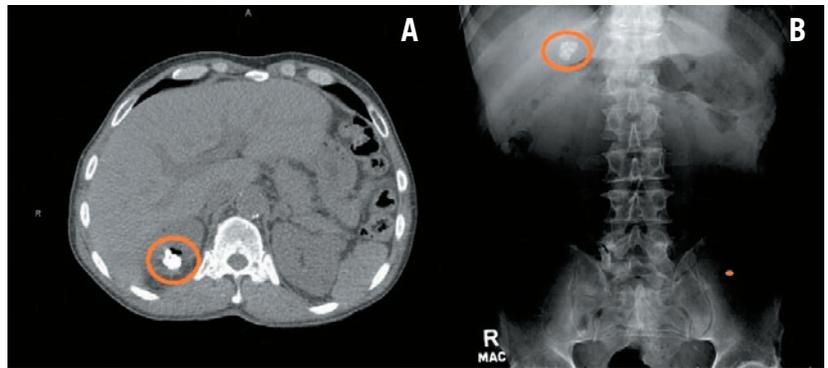


FIGURE 1 Non-Contrast CT Scan Imaging of the Abdomen and Pelvis. Single-view kidneys, ureters, and bladder (KUB) radiography (A); depicting a cluster of multiple intra-renal kidney stones measuring 2–3 cm within an upper pole calyceal diverticulum (red circle) (B).

Given the incidental primary squamous cell carcinoma within the upper pole calyceal diverticulum of the right kidney with a positive focal surgical margin at the base of the partial nephrectomy resection site, what is the most appropriate next step in management?

- A. Observation with surveillance imaging
- B. Repeat right partial nephrectomy with negative histological margins
- C. Salvage right radical nephrectomy
- D. Adjuvant systemic therapy
- E. Adjuvant radiation to the right kidney

➔ **TURN TO PAGE 70** for the answer and a discussion of this case by experts.

pelvis with intravenous contrast was obtained, revealing a 2–3 cm cluster of renal stones within a calyceal diverticulum at the upper pole of the right kidney. Cross-sectional imaging showed

no other stones and/or masses, with a normal contralateral left kidney.

After discussing potential treatment options with the patient, including the risks and benefits, a right robotic-

CORRECT ANSWER: C. Salvage right radical nephrectomy

Continued from page 69

assisted laparoscopic upper pole partial nephrectomy was selected. During the procedure, the calyceal diverticulum was extracted, and residual kidney stones were removed en bloc with renorrhaphy; the collecting system was also closed. A 1-cm margin of normal renal parenchyma was also taken deep to the calyceal diverticulum during the resection. The surgery was successful, with no postoperative complications, and the patient was discharged 2 days later.

The kidney stones were calcium oxalate monohydrate in nature. However, follow-up histopathological evaluation of the resected tissue revealed poorly differentiated carcinoma arising from the right upper pole calyceal diverticulum with invasion through the urothelial wall into the underlying renal parenchyma, with a 2–3 mm focal positive surgical margin at the base of the partial nephrectomy resection site. Microscopic examination of the tissue by our pathologist revealed keratin pearl formation, intercellular bridges, and keratotic debris, and immunohistochemical staining demonstrated strong positivity for p63 (**Figure 2**). Based on these findings and the patient's clinical history, a diagnosis of primary squamous cell carcinoma (SCC) of the right kidney was established.

Discussion

Primary SCC of the renal pelvis and kidney is a very rare neoplasm, accounting for less than 1% of all malignant renal neoplasms. [1] SCC of the kidney occurs in men and women equally, particularly those between the ages of 50 and 70 years. [2] Most often, the etiology of SCC is long-standing nephrolithiasis, especially the formation of staghorn renal calculi. [3] The mechanism of carcinogenesis is assumed to be

secondary to chronic irritation, inflammation, and/or infection, all of which can lead to squamous metaplasia. Other risk factors, such as hydronephrosis, vitamin A deficiency, chemical use, and hormonal imbalances, have also been implicated in the development of SCC of the kidney. [4,5] It is also worth noting that the incidence of renal SCC is higher in individuals with horseshoe kidneys. [6]

SCC of the kidney tends to be large, necrotic, sessile, ulcerated, and infiltrative of the renal parenchyma, as well as the perinephric soft tissue. [3] Diagnosis of this malignancy is restricted to tumors that

rare, it should be distinguished from metastatic SCC based on the patient's clinical history, imaging, and histopathology. [9]

Establishing a diagnosis via imaging is difficult because SCC of the kidney exhibits no specific radiological features; in addition, given the rarity of this disease, other diagnoses, such as transitional cell/urothelial carcinoma of the renal collecting system or a complex kidney cyst, are much more likely. [10] The use of 18-fluorine fluorodeoxyglucose (18F-FDG) PET/CT imaging has been reported to be most helpful in confirming the diagnosis of these renal tumors, with a sensitivity of 62% and a specificity of 88%, although imaging cannot differentiate disease stage or grade. [11] For extra-renal SCC lesions, the sensitivity and specificity of

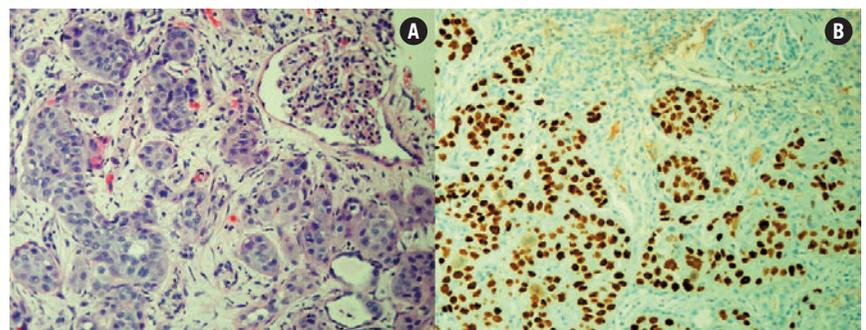


FIGURE 2 Histopathological Evaluation of Renal Squamous Cell Carcinoma. H&E staining demonstrating malignant squamous cells (left) adjacent to a normal glomerulus (right; magnification, 200×) (**A**); with specialized immunohistochemical staining that is intensely positive for p63 (magnification, 200×) (**B**).

show squamous differentiation and histological hallmarks of SCC, such as keratin pearl formation, intercellular bridges, and keratotic debris. [7] However, because most tumors are moderately or poorly differentiated, these characteristics may not be obvious. [3] Lee et al devised the classification of renal SCC as one of two groups: central or peripheral. [8] Central renal SCC is more intraluminal and is usually associated with metastases to the lymph nodes, while peripheral renal SCC is prominent in the renal parenchyma and may invade the perirenal fat before metastasizing to the lymph nodes or a distant site. Since primary SCC of the kidney is

18F-FDG PET/CT increase to 84% and 91%, respectively, making this imaging much more useful for non-renal primary sites. [11] Overall, however, imaging is not helpful in determining the histology of primary SCC of the kidney, and diagnosis is typically made after nephrectomy.

Primary renal SCC tends to manifest at a more advanced disease stage compared with transitional cell/urothelial carcinomas and/or renal cell carcinomas, most likely due to the underlying aggressive nature of SCC, the reduced prevalence of symptoms such as hematuria or flank pain, and the lack of a measurable tumor marker in the urine or serum. Therefore,

the prognosis of primary SCC of the kidney is, on average, incredibly poor, with the majority of patients presenting with locally advanced or metastatic disease and limited long-term survival.[12] Although the incidence of warning signs is low, patients may experience a constellation of symptoms, including flank or abdominal pain, hematuria, fever, weight loss, or an abdominal mass, and patients are occasionally diagnosed with localized disease incidentally.[13] Renal SCC may also be associated with paraneoplastic syndromes, such as hypercalcemia, due to the ectopic secretion of parathyroid hormone–like substances.[14]

Very little long-term data on renal SCC exist in the literature, the majority of which is contradictory. In addition, no gold standard of management exists, with many treatments being anecdotal or based on other SCC tumor sites.[12] For clinically nonmetastatic, localized primary SCC of the kidney, the best known treatment is surgical resection with radical nephrectomy (**Answer C**). This is because partial nephrectomy, especially in the setting of positive histological margins, is unlikely to be curative and carries a high risk of recurrence within the kidney due to the diffuse, infiltrative nature of SCC into the renal parenchyma and perinephric soft tissue (**Answer B**). Active surveillance with serial imaging would also not be warranted, even for smaller foci of SCC within the kidney, due to the aggressive nature of this disease and a lack of reliable imaging to accurately predict the extent of disease (**Answer A**).

Although surgical resection is rarely curative, adjuvant chemotherapy or radiation is usually ineffective for renal SCC (**Answers D and E**).[3] The most common chemotherapy agents used to treat this condition are platinum-based,

Key Facts: Renal Squamous Cell Carcinoma

- Primary renal squamous cell carcinoma (SCC) is an extremely rare malignancy of the kidney, most often associated with long-standing nephrolithiasis, especially the formation of staghorn kidney stones, due to chronic irritation, inflammation, and/or infection, all which can lead to squamous metaplasia.
- Manifestation of primary renal SCC tends to occur at an advanced disease stage, with locally infiltrative and/or metastatic tumors that are difficult to accurately identify on imaging.
- The prognosis of renal SCC is poor, with an average median survival of less than 1 year. No proven survival benefit has been seen with the use of adjuvant chemotherapy or radiation treatment after surgical resection.

with radiation most often reserved for palliative purposes in patients with metastatic disease and severe local symptoms. Currently, the combination of cisplatin, methotrexate, and bleomycin is employed for these individuals, but no benefit in survival has been observed.[4] One study reported a median survival of 7 months postoperatively, with a 5-year survival rate of 7.7%, but another demonstrated a median survival as low as 3.5 months.[3,7] In a large meta-analysis by Berz et al analyzing survival among patients with

squamous cell malignancies of the upper urinary tract, the authors reported that the median overall survival time was 10 months compared with 63 months for transitional cell/urothelial histology.[12] Although the prognosis of renal SCC can be equivalent to transitional cell/urothelial carcinoma with appropriate treatment throughout each stage of disease, the average survival for primary SCC of the kidney is comparatively much worse due to more advanced disease at the time of presentation.[3]

Outcome of This Case

The patient underwent salvage right robotic-assisted laparoscopic radical nephrectomy 2 months after his initial right partial nephrectomy with calyceal diverticulectomy surgery. His postoperative course was uncomplicated, and he was discharged home on postoperative day 2. Final histopathological analysis of the remaining right kidney revealed residual pT3a primary SCC with microscopic perinephric fat invasion with negative surgical margins circumferentially and no evidence of vascular invasion. No adjuvant treatment was given.

Currently, the patient is doing well 6 months after salvage right radical nephrectomy. He has remained recurrence-free based on cross-sectional surveillance imaging with contrasted CT scan of the chest, abdomen, and pelvis at 3 and 6 months postoperatively. Periodic imaging with follow-up will be continued every 3 months for the first year. ■

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➤ For references visit cancernetwork.com/renal-SCC-CQ



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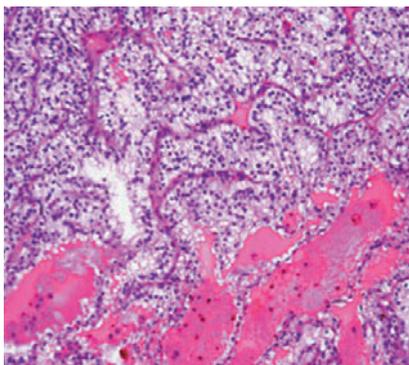
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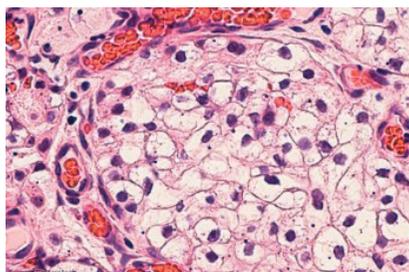
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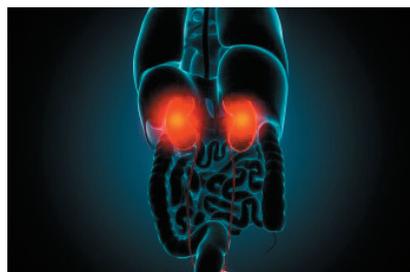
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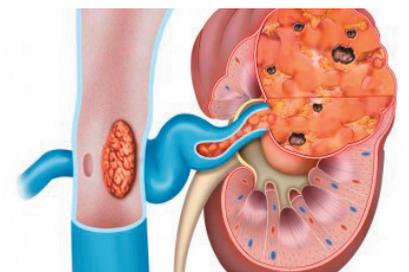
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MEET OUR EXPERT



Dr. Copelan is Chair of the Department of Hematologic Oncology and Blood Disorders at the Levine Cancer Institute in Charlotte, North Carolina.

CAR T-Cell Therapy in Non-Hodgkin Lymphoma Patients

Dr. Copelan discusses the use of chimeric antigen receptor (CAR) T-cell therapy in non-Hodgkin lymphoma (NHL) patients and how these therapies might improve upon the current standard of care.

Q: Both tisagenlecleucel and axicabtagene ciloleucel are approved by the US Food and Drug Administration for the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma. Are there specific patients for whom these therapies are most suited? How do you decide which patients are the best candidates for CAR T-cell therapy?

DR. COPELAN: The first criterion that helps identify appropriate patients for these treatments is that CAR T-cell therapy is confined right now to those patients who have relapsed or

refractory disease. These patients are unlikely to respond to standard treatments. We then try to restrict this therapy to patients who can tolerate the potential side effects of CAR T cells. For instance, cytokine release syndrome is a significant side effect of CAR T cells in many patients, and if patients have significant comorbidities, they are less likely to tolerate this treatment and the toxicities.

In addition, these patients can develop cerebral edema and other neurotoxicities that, again, if they have significant comorbidities, are more likely to lead to poor outcomes. So, we try to restrict CAR T cells to patients who we think could

PERSPECTIVE

Brian Till, MD, discusses challenges and promise on page 74.

tolerate the toxicities of this treatment.

Q: In your experience, what have been the challenges with these approved CAR T-cell therapies so far? Is access an issue, for example?

DR. COPELAN: Access is a big problem. It is very clear that most patients who would be eligible and could benefit from

KEY QUESTION

How have the approval and availability of these therapies changed the way you and your colleagues think about treating NHL, in terms of choosing a first line and subsequent lines of therapy, including stem cell transplants?

DR. COPELAN: These therapies are not first-line therapies at this point, and it is important that our current first-line therapies are effective in a substantial proportion of patients. Most patients who have been treated thus far have failed at least two prior lines of therapies. These patients are highly unlikely to have meaningful responses to traditional agents, but a substantial proportion of the patients we've treated with CD19-directed CAR T cells have had responses, most of which have been long-lived. Thus, compared with standard therapies in this setting—that is, for relapsed/refractory patients—CAR T cells appear to be so much more effective than other therapies that there is now a study that is assessing their value when given earlier in the course of disease, including in comparison with autologous transplantation.[1]



PERSPECTIVE BY

Brian Till, MD

CAR T-Cell Therapy: Challenges and Promise

Chimeric antigen receptor (CAR) T cells have emerged as a highly effective treatment for patients with relapsed or refractory aggressive B-cell lymphomas and B-cell acute lymphoblastic leukemia. Challenges do remain with respect to toxicity, access, cost, and insurance coverage, as Dr. Copelan pointed out. Additionally, despite the high response rates, resistance to CAR T-cell therapy or relapse after an initial response remain problems for a significant proportion of patients. However, I am optimistic that as our collective experience with CAR T cells accumulates, we will see improvement in these areas.

With respect to safety, as we gain proficiency in managing cytokine release syndrome (CRS), adverse outcomes should keep decreasing. A deeper understanding of the biology of CRS and neurologic toxicity should also lead to more effective and targeted interventions for treating and even preventing these complications. Improved manufacturing techniques may also influence continued advances in safety. For example, administering cell products formulated with a defined ratio of CD4:CD8 cells seems to be associated with lower toxicity rates, without a loss of efficacy, as suggested by preliminary data from the multicenter TRANSCEND study testing lisocabtagene maraleucel.

We may learn that manufacturing techniques enhance treatment efficacy as well. The group at University of Pennsylvania recently showed, for example, that shortening the culture time of CAR T cells to 3 to 5 days led to improved antitumor function in a mouse model. Another approach being investigated to improve efficacy is targeting multiple antigens, which may help to reduce relapse rates by preventing antigen loss escape. In addition to targeting CD19 in combination with CD22, which Dr. Copelan mentioned, at least one trial is exploring dual targeting of CD19 and CD20. In addition, CARs targeting other antigens are being investigated that could potentially be combined in the future. Perhaps the largest gains in efficacy will come from a better understanding of the biology underlying CAR T-cell interactions with the tumor microenvironment, which may point to ways of overcoming tumor resistance in patients refractory to CAR T-cell therapy.

Finally, cost remains an issue. However, some cost-benefit analyses have shown that these treatments can potentially be cost effective, and more such studies are needed. As CAR T-cell therapies become more efficacious, grow potentially cheaper as competition increases, and can prevent the need for many lines of costly salvage therapies, the costs of treatment may prove to be a good investment for healthcare payers. This may be particularly true if ongoing trials show a superiority of CAR T cells over autologous stem cell transplantation as first-line salvage for diffuse large B-cell lymphoma.

FINANCIAL DISCLOSURE: Dr. Till has patents with, and receives royalties and research funding from, Mustang Bio.

Dr. Till is Associate Professor of Medicine, University of Washington, Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center, and Attending Physician, Seattle Cancer Care Alliance, Seattle, Washington.

these drugs and clinical trials are not referred to the institutions that have access to them. Another challenge is the financial ramifications. These treatments are incredibly expensive, even compared with other novel treatments, and often insurers don't adequately cover them and the expenses associated with their use. So, aside from the toxicities of the drugs, there are other significant problems to overcome.

Q: Could you highlight some of the ongoing NHL clinical trials that could potentially move CAR T cells into earlier or additional lines of therapy?

DR. COPELAN: As I mentioned, the initial studies were for relapsed/refractory patients, and many of these patients relapsed after transplantation or did not qualify for transplantation on the basis of not responding to chemotherapy.[2,3] So, again, these are the patients with poor prognoses. Current ongoing trials and those in development are and will be testing these agents in the second line and comparing them vs autologous transplant. The multicenter trial in relapsed patients that I mentioned previously is comparing standard chemotherapy and transplantation, which is the traditional and standard treatment for NHL, vs CAR T-cell therapy in a large study that requires a lot of patients and likely will take some time to complete. Eventually, it will tell us whether CAR T cells should be introduced earlier in the course of disease.[1]

Q: Lastly, are there additional novel CAR T-cell therapies in clinical trials for NHL, besides tisagenlecleucel and axicabtagene ciloleucel?

DR. COPELAN: Yes, the most intriguing aspect of CAR T cells is that they have only been around clinically for a short while, so clinicians have understandably focused on the CAR T cells that we are currently using. However, there are basic improvements in CAR T cells that are being developed in the lab, and will be studied mainly in single-institution trials, which in my mind will make CAR T-cell therapy much better. For example, one of the obstacles for CAR T-cell patients who relapse is that the

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MEET OUR EXPERT



Dr. Herrmann is the Director of the Cardio-Oncology Clinic at Mayo Clinic in Rochester, Minnesota. He is also a Consultant and Chair for Research, Division of Ischemic Heart Disease and Critical Care, Department of Cardiovascular Medicine, also at Mayo Clinic.

Detecting Cardiotoxicity in Cancer Patients Receiving VEGF Inhibitors

The treatment of cancer patients with vascular endothelial growth factor (VEGF) therapy is sometimes associated with cardiotoxicity. Therefore, it is important that clinicians understand the predictors of these adverse effects and learn how best to monitor for them. In this interview, *ONCOLOGY* spoke with Joerg Herrmann, MD, a cardiologist at the Mayo Clinic who evaluates and treats patients with cancer and heart disease.

Q: How do VEGF inhibitors work? What are the associated cardiotoxicities that have been documented

with these agents in clinical trials?

DR. HERRMANN: VEGF inhibitors go back to Dr. Judah Folkman's great vision of antagonizing angiogenesis, including the critical role that angiogenesis plays in cancer growth and metastasis. VEGF is one of the cardinal angiogenesis factors that tumors use to develop their vasculature, thereby aiding in the growth and development of cancer. Therefore, antagonizing VEGF with VEGF inhibitors was a conceptual breakthrough that also translated into clinical improvement.

Bevacizumab is one such VEGF inhibitor used to treat

PERSPECTIVE

Roohi Ismail-Khan, MD, MSc, discusses benefits of cardio-oncology programs on page 76.

a number of cancers. Despite the fact that it is one of the best-selling drugs of all time, it has been associated with several toxicities—some that were expected and some that were not. These include hypertension, ischemic events, thrombotic events, both arterial and venous events, bleeding events, cardiac dysfunction, and heart failure.[1]

KEY QUESTION

Do certain comorbidities preclude patients from receiving anti-VEGF therapy? In addition, do certain cardiac conditions increase the risk of cardiotoxicity from VEGF inhibitors?

DR. HERRMANN: Studies have shown that the predictors of cardiotoxicity are coronary heart disease and hypertension. When encountering patients with these conditions in the clinic, you should carefully discuss the risks and benefits of VEGF inhibitors. It is worth noting that a bit of debate surrounds the actual risk, as in how many patients a clinician needs to actually treat before seeing that kind of harm. A meta-analysis published in 2017 found that about 140 patients need to be treated before seeing one with cardiac dysfunction, and 410 patients need to be treated before seeing one with clinical heart failure.[2] I think it is important to mention these numbers and to put the benefits vs risks of these therapies into perspective. They can have huge benefits and we don't want to overstate the risks, but we should be realistic. More than 1,200 patients need to be treated before a fatal event occurs. This, too, puts the risk-benefit conversation in perspective.

In the clinic, we need to counsel patients about these risks and ensure that their blood pressure is well-controlled. High blood pressure may cause sub-endocardial ischemia, which can evolve with increased pressure in the heart chamber alone. Myocardial ischemia can also be triggered by a significant stenosis in the coronary artery. Therefore, a stress test and treatment of such conditions should be completed before initiating VEGF inhibitor therapy. Since no randomized clinical trials or other evidence are currently available to support these recommendations, they are more of a consensus by the experts in the field.



PERSPECTIVE BY

Roohi Ismail-Khan, MD, MSc

The Benefit of Cardio-Oncology Programs for Cancer Patients

Cardio-oncology is a cutting-edge, multidisciplinary field focusing on the management and prevention of cardiovascular complications in cancer patients and survivors. Although survival rates for cardiovascular disease and cancer have improved dramatically, these conditions are still the two biggest killers of patients today. Cardiac toxicity is the second most common cause of morbidity and mortality in cancer survivors. Despite advances in both fields, many cancer patients experience cardiovascular complications as a result of cancer therapy. In addition, a large proportion of patients with pre-existing cardiovascular disease require cardiotoxic therapy for cancer.

In this interview, Dr. Herrmann perfectly describes the cardiotoxicity associated with vascular endothelial growth factor (VEGF) inhibitors. Although VEGF inhibitors pose a risk of cardiovascular toxicity, they may significantly improve progression-free survival (PFS). Simply put, new blood vessel formation (angiogenesis) is critical for the growth of tumors, and anti-angiogenic therapy assists in tumor regression. Bevacizumab, a humanized monoclonal antibody directed against VEGF, was the first targeted angiogenesis inhibitor to be developed. Since its approval in 2004, it has become one of the top ten best-selling drugs *of all time*. In patients with colorectal cancer and non-squamous-cell lung cancer, the addition of the angiogenesis inhibitor bevacizumab *doubled* PFS. Similarly, in patients with metastatic renal cell carcinoma, sunitinib (another VEGF inhibitor) *more than doubled* overall survival.

Interestingly, in breast cancer,

bevacizumab was granted accelerated approval in 2008 based on the E2100 trial, which showed that treatment with bevacizumab led to a 5.5-month improvement in PFS. However, the drug was associated with serious cardiotoxicity. Two subsequent studies, AVADO and RIBBON-1, showed only a slight effect on tumor growth with no benefit in OS compared with standard chemotherapy. Therefore, on November 18, 2011, the US Food and Drug Administration (FDA) withdrew bevacizumab's breast cancer indication after concluding that it had not been shown to be safe and effective for the treatment of breast cancer. The FDA's decision was met with mixed emotions among patients and healthcare professionals, including many breast oncologists like myself who had seen solid success stories in the clinic. Could it be that if we proactively monitored, managed, and controlled the cardiovascular side effects during treatment of our patients on bevacizumab, as Dr. Herrmann suggests, that we would still be using this drug in breast cancer patients today?

The cardiovascular toxicities associated with bevacizumab include both vascular and cardiac side effects, which are based on the role VEGF plays in the development and functional integrity of the vasculature, as well as the importance of the vasculature to heart function. The spectrum of toxicity of bevacizumab in the literature spans from hypertension to atherosclerosis, arterial and venous thrombotic events, and heart failure.

Various other novel drugs and targeted therapies used to treat cancer also have cardiovascular side effects. Many of these drugs may cause newly

diagnosed cardiovascular problems, or can exacerbate previously identified cardiovascular disease. The rate of cardiotoxicity from cancer-related therapeutics has been reported to be greater than 30%, with some events occurring many years after therapy completion.

All of these facts necessitate the existence of a cardio-oncology program, in which oncologists and cardio-oncologists work together to manage patients. The initial focus of cardio-oncology was on heart failure associated with anthracycline use. However, increasingly utilized novel anticancer agents—such as VEGF inhibitors, tyrosine kinase inhibitors, cyclin-dependent kinase inhibitors, and various immunotherapy treatments—are associated with many other cardiotoxicities beyond heart failure, including hypertension, arrhythmias, thromboembolic disease, vascular disease, and coronary disease.

Given these complexities, it is important that patients have access to providers who possess knowledge of both cardiovascular disease *and* cancer therapeutics. This multidisciplinary approach to treating patients is why the field of cardio-oncology is growing by leaps and bounds; it is also why a number of academic and community programs have embraced this approach. Going forward, smart management and treatment of cancer therapy-related cardiac dysfunction can have a profound impact on improving morbidity and mortality in cancer patients.[1]

FINANCIAL DISCLOSURE: Dr. Ismail-Khan has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➤ For references visit cancernetwork.com/VEGF-cardiotoxicity

Dr. Ismail-Khan is a Medical Oncologist and Co-Director of the Cardio-Oncology Program at H. Lee Moffitt Cancer Center, Tampa, Florida, where she works with the University of South Florida Director of the program, Michael Fradley, MD.

Q: Some of these cardiotoxicities are part of the mechanism of the VEGF agents. However, do VEGF inhibitors also cause off-target effects?

DR. HERRMANN: Yes, indeed. VEGF is critical for the development of new vessels, a process called neovascularization. However, it has been debated how important VEGF is to adults with developed vasculature. Research has shown that it does still play a role in these individuals, especially in the endocrine organs and for those with fenestrated capillaries (ie, the thyroid and other endocrine glands). These vessels regress quite rapidly following VEGF inhibitor therapy, but they also regrow following the end of therapy.

Since the heart is not subjected to as much growth inhibition and regrowth as endocrine organs, we don't see the same regression there. However, it is critically im-

portant that the VEGF-driven compensatory angiogenesis response occurs when the heart is subjected to increased afterload. Most of the time, the cause of an increased afterload is increased blood pressure or uncontrolled hypertension, but aortic stenosis or inhibiting VEGF in this setting can also be detrimental. There are several other conditions that may predispose patients to this phenomenon that occurs as part of the mechanism of these VEGF agents.

Q: How, specifically, should patients taking VEGF inhibitors be monitored for cardiac toxicities?

DR. HERRMANN: All patients taking VEGF inhibitors should be monitored for cardiotoxicities. According to the 2014 American Society of Echocardiography and the European Association of Cardiovascular Imaging consensus recommendations, patients undergoing

VEGF inhibitor therapy should undergo an echocardiogram after the first month of therapy and then every 3 months thereafter.[3] This is because any drop in ejection fraction can sometimes be seen early after initiating anti-VEGF therapy. It also supports the idea that the myocardium plays a compensatory role that evolves very early on, and, while it may not be directly cardiotoxic, it can evolve along the vascular concept of cardiomyopathy. We also have to be cognizant that cardiovascular effects can occur later on, which is why screening every 3 months is recommended. Another important component observed from clinical practice is that about 50% to 60% of patients will have reversibility of the drop in ejection fraction. This provides more impetus to conduct these surveillance echocardiograms, since we can truly alter the course and prevent heart failure.

Of note, several of the tyrosine kinase inhibitors can cause QTc prolongation. It is recom-

mended that an electrocardiogram be obtained regularly, maybe after 2, 4, and 8 weeks. This can be done at longer intervals after patients have been on therapy for a while with no events. In addition, blood pressure should be monitored very closely in these patients, particularly in the first few weeks when most changes are seen following the first cycles of treatment. There has been some thought about whether ambulatory blood pressure monitoring should be utilized in this population. However, it can also be done with whole blood pressure measurements and office measurements. These are the cardinal elements for serial surveillance: echocardiography, electrocardiography, and blood pressure measurements. ■

FINANCIAL DISCLOSURE:

Dr. Herrmann received unrelated research support from Amgen.

➤ For references visit cancernetwork.com/VEGF-cardiotoxicity

CAR T-Cell Therapy in NHL

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tumor can escape recognition by the CAR T cell by loss of expression of the antigen to which the CAR T cells are directed, which is CD19. One important approach has been to develop dual-targeted CARs so that the CAR T cells will be directed not only to CD19, but also to CD22, which is another protein expressed by B-cell malignancies. There are also studies on CD22-directed CAR T cells to see if these are

better than the CARs we are making now.[4,5]

In addition, there are basic studies using gene editing to insert the CAR gene uniformly at the T-cell receptor alpha chain constant region as opposed to current random integration, which results in variable expression in which cells with less expression may be less effective, and others with higher expression suffer tonic CAR

signaling and exhaustion. [6] Alternatively, exhausted CARs might be rescued by checkpoint inhibition or other approaches. Thus, some of the current problems limiting the effectiveness of CARs could most likely be overcome by basic progress in the lab right now, which then will evolve into studies at individual institutions. We might be a few years away from multi-institution studies, but these advances will almost certainly dramatically improve the effectiveness and

toxicities of CAR T cells. I am really most excited about the basic studies in the lab and the small institutional studies right now, which are sure to improve CARs and their application to patients. ■

FINANCIAL DISCLOSURE:

Dr. Copelan has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➤ For references visit cancernetwork.com/CAR-T-cell-NHL

The Microbiome and Colorectal Cancer: Current Clinical Trials

Jennifer Leavitt, MS, and Naveed Saleh, MD, MS

BACKGROUND: Colorectal cancer (CRC) is a leading cause of mortality in Western countries. It is the third most prevalent lethal cancer in the United States for both genders. Despite an overall decline, CRC is on the rise in young and middle-aged adults. Compared with people born in 1950, those born in 1990 have double the risk of colon cancer and are four times more likely to develop rectal cancer.[1] Long-term research points to genetic, environmental, and dietary factors as influential in the development, progression, and recurrence of CRC. More recent evidence suggests a correlation between intestinal microbiota composition and CRC, though no pattern of cause and effect has yet been identified.[2]

Researchers are exploring nutritional and other interventions to determine whether altering the gut microbiome can influence colorectal cancer. Following are several clinical trials in this discipline that are currently recruiting or will be recruiting in the near future.

Survivors

Beans to Enrich the Gut Microbiome vs Obesity's Negative Effects (BE GONE) Trial
ClinicalTrials.gov Identifier: NCT02843425
(Recruiting)

University of Texas MD Anderson Cancer Center, Houston, TX

Enrolling survivors with a previous history of colorectal cancer and MD Anderson patients who have had a precancerous colorectal polyp, and who have a current adult body mass index (BMI) of 25 or higher. This investigational study aims to determine whether eating canned, precooked beans can help improve the levels of healthy bacteria in the digestive system and reduce the effects of obesity on cancer risk.

Food and Microbiome Longitudinal Investigation (FAMiLI)

ClinicalTrials.gov Identifier: NCT03293758
(Recruiting)

New York University School of Medicine, New York, NY

Enrolling patients with a diagnosis of colon cancer. The study cohort is designed to improve understanding of the role of the human microbiome in health and disease.

Gut Microbiome in Fecal Samples from Patients with Metastatic Cancer Undergoing Chemotherapy or Immunotherapy

ClinicalTrials.gov Identifier: NCT02960282
(Recruiting)

University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA

Enrolling patients with metastatic disease. This trial focuses on studying the gut microbiome via fecal samples from patients with metastatic disease and who are undergoing chemotherapy or immunotherapy. Researchers seek to understand whether the make-up of the gut microbiome has a positive or negative influence on a patient's response to these therapies.

Metabionics Colon Cancer Clinical Research Study
ClinicalTrials.gov Identifier: NCT02151123 (Not yet recruiting)

University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO

Enrolling patients diagnosed with CRC. This clinical research aims to investigate the association of the gut microbiome with colonic neoplasia. Several types of gut microbiome samples will be collected from patients undergoing colectomy for colonic adenocarcinoma; these samples will be tested by the Metabionics Colon Polyp and Colorectal Cancer Assay, and the percentage of false-negative results determined.

Metagenomic Evaluation of the Gut Microbiome in Patients with Lynch Syndrome and Other Hereditary Colonic Polyposis Syndromes

ClinicalTrials.gov Identifier: NCT02371135
(Recruiting)

Memorial Sloan Kettering Cancer Center, New York, NY

Enrolling patients with Lynch syndrome or other hereditary colonic polyposis syndromes. The study's purpose is to understand the role that bacteria that normally live in the colon may play in colorectal cancer risk, in addition to the hereditary risk and potential dietary impact. Investigators will collect stool specimens, additional colon biopsy specimens, and questionnaire responses on diet and lifestyle.

Pilot Trial of Resistant Starch in Stage II-III

Colorectal Cancer Survivors

ClinicalTrials.gov Identifier: NCT03781778 (Not Yet Recruiting)

Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington

Enrolling patients diagnosed with stage II-III colorectal adenocarcinoma. This phase II pilot trial aims to understand the effect of resistant starch consumption on the gut microbiome and on biomarkers potentially related to colorectal cancer

progression. A comparison will be made against consumption of foods made with corn starch.

Healthy Volunteers

Diet Modulation of Bacterial Sulfur and Bile Acid Metabolism and Colon Cancer Risk
ClinicalTrials.gov Identifier: NCT03550885
(Recruiting)

Rush University Medical Center/University of Illinois at Chicago, Chicago, IL

Enrolling adult African American women with a BMI 30 to < 50, 45-75 years of age, with elevated c-reactive protein and at increased risk for CRC. The study's goal is to determine the extent to which a relationship between diet (independent variable) and mucosal markers of CRC risk can be explained by the abundance of sulfidogenic bacteria and hydrogen sulfide (H₂S) concentrations &/or deoxycholic acid (DCA) and DCA-producing bacteria *clostridium scindens* (mediator variables).

Fiber to Reduce Colon Cancer I Alaska Native People

ClinicalTrials.gov Identifier: NCT03028831
(Recruiting)

Alaskan Native Tribal Health Consortium, Anchorage, AK

University of Pittsburgh, Pittsburgh, PA

Enrolling Alaska Native people (ANs), ages 40-65 years, with a BMI between 18-35. This double-blind, placebo-controlled study aims to determine whether, despite a high consumption of anti-inflammatory and antineoplastic n-3 fish oils, ANs are at increased risk of colon cancer because of colonic butyrate deficiency resulting from a remarkably low consumption of fiber-containing foods. Results will be used as the scientific basis for a definitive large-scale high-fiber supplementation study (to achieve > 50 g total fiber/d) to suppress adenomatous polyp recurrence following colonoscopy.

Omega-3 Fatty Acid for the Immune Modulation of Colon Cancer (OMICC)

ClinicalTrials.gov Identifier: NCT03661047
(Recruiting)

Harvard School of Public Health/Massachusetts General Hospital, Boston, MA

Enrolling those with confirmed or suspicion of adenocarcinoma, ages 18-75 years. This prospective, double-blind, placebo-controlled, stratified, randomized clinical trial will assess effects of daily 4-g random marine omega-3 polyunsaturated fatty acid (MO3PUFA), through treatment with AMR101 (VASCEPA, icosapent ethyl) on the tumor immune microenvironment and gut microbiome.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

➔ For references visit
cancernetwork.com/microbiome-CRC-trials

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A woman is shown from the chest up, wearing a light blue hairnet and a white hospital gown with a blue diamond pattern. She is looking upwards and to the right with a thoughtful expression. The background is solid black.

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