

Development and Implementation of an Academic Cancer Therapy Stewardship Program

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Antibiotic stewardship programs are an integral part of infectious disease management. Such programs have been shown to reduce resource overutilization, costs, drug resistance, and prescribing errors, thereby improving overall quality and value in healthcare.¹⁻⁴ A similar program designed to help guide cancer treatment has never been described in the medical literature to date.

Cancer care makes up a sizable portion of US healthcare expenditures, which continue to increase despite recent reforms. According to CMS, total US healthcare spending in 2014 increased 5.3% from the previous year to \$3 trillion.⁵ The cost of cancer care alone, estimated at \$125 billion in 2010 and projected to reach \$158 billion by 2020, is a significant contributor to this total.⁶ This issue is garnering more attention from both the healthcare sector and the public, especially as it relates to the soaring costs of cancer drugs.⁷ Indeed, Kantarjian et al showed that the average price of new antineoplastic agents doubled from 2003 to 2013, rising from \$4500/month to more than \$10,000/month.⁸ These price increases have become difficult to justify because a correlation between the cost of a given cancer drug and its relative benefit, as measured by a number of validated parameters, is often lacking.⁸ Regrettably, a majority of the cost of cancer treatment often eventually falls on patients and their families, resulting in substantial financial burdens.

In response to this situation, discussions about value-based cancer care have become increasingly common. Many leaders in oncology, including the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network, have been very active in these discussions, releasing consensus statements, drafting policy, and leading lobbying efforts. For example, in 2015, ASCO developed its "Conceptual Value Framework," a tool meant to help physicians and patients assess the value of novel antineoplastic agents based on clinical benefits and potential toxicities, all within the context of cost.⁹

The concepts of value-based care and cost-consciousness have also become essential to hospitals and health systems as they grapple with the challenges of an evolving reimbursement environment.

ABSTRACT

OBJECTIVES: Antibiotic stewardship is an integral aspect of hospital care, limiting the potential for resistance while working to minimize waste. A similar system is needed in oncology, given the rapid proliferation of new therapies and the challenges of navigating a complicated reimbursement environment. A "cancer therapy stewardship program" has never been described in the literature. Here, we detail our efforts to design and implement such a program and share lessons learned to inform future projects.

STUDY DESIGN AND METHODS: For 1 year, a hematologist-oncologist (the "cancer therapy steward") at Mount Sinai Hospital was in charge of addressing all requests for nonformulary or off-label chemotherapeutic and supportive medications and regimens. Requests consisted of the rationale for use and supporting data from medical journal articles. This pilot initiative was focused mainly on inpatient malignant hematology.

RESULTS: Sixty-seven requests were made by 23 physicians, and all requests were ultimately approved. Requests tended to fall into 3 categories: 1) use of a single drug in a setting not approved by the FDA, 2) use of multiple drugs in novel combinations not approved by the FDA, and 3) adding novel drugs to existing FDA-approved regimens.

CONCLUSIONS: Our cancer therapy stewardship program yielded many useful insights into how our physicians face challenging clinical situations. It also helped to improve overall clinical quality and patient care by emphasizing the importance of value-based care and evidence-based medicine. Expanding this program will likely lead to many interesting experiments aimed at improving medical education and research, patient safety outcomes, and clinical quality.

Am J Manag Care. 2018;24(3):147-151

TAKEAWAY POINTS

A cancer therapy stewardship program can be used to improve clinical quality and patient care by emphasizing the importance of value and evidence in oncology.

- ▶ This is the first known description of applying the idea of drug stewardship to oncology.
- ▶ We share several important insights gained and lessons learned, which have real-world implications for healthcare institutions, especially in terms of quality improvement.
- ▶ This research builds a foundation upon which further work in this area may begin, including studies focusing on cost-effectiveness and clinical quality innovation.
- ▶ Benefits realized from this type of work may have broader implications, including at the healthcare policy level.

The importance of these ideas in oncology is illustrated by the rise of the bundled payment and diagnosis-related group systems, which outline reimbursement policies within the context of value and cost. As an example, the setting in which a patient receives cancer treatment usually determines the reimbursement for the institution, with outpatient treatment generally being reimbursed at higher rates. Such policies provide additional incentive for healthcare systems to emphasize outpatient, as opposed to inpatient, cancer care.

Despite the many reasons for preferentially giving cancer therapy in the outpatient setting, circumstances do occasionally arise that require inpatient treatment. Perhaps the most common scenario is when a patient experiences a complication or crisis secondary to cancer progression. We hypothesize that, as with antibiotic stewardship programs, there are significant potential benefits to developing an institutional system to monitor and regulate the use of cancer treatments in all clinical settings. Here, we aim to describe our efforts to design and implement a “cancer therapy stewardship program” at our institution and to share lessons learned in order to inform future work in this new and evolving area.

METHODS

Mount Sinai Hospital is a major tertiary care teaching facility and regional referral center with 1171 inpatient beds and National Cancer Institute designation. There are 2 committees in place to work with physicians who treat cancer. The Oncology Pharmacy/Therapeutics Subcommittee reviews requests from providers for the hospital to add certain oncology-related medications to the hospital formulary. The Chemotherapy Council evaluates various cancer treatment regimens and decides whether or not they should be built into our computer-based chemotherapy ordering system to facilitate their use. Both groups are composed of physicians, nurses, and pharmacists.

We developed this stewardship program after hypothesizing that adding a layer of oversight specifically for the use of nonformulary or off-label cancer therapies and regimens at our institution may help optimize clinical efficiency and value. Although both of the committees described above peripherally address this issue, their main concerns

have to do with the system-wide availability of these therapies, both in the formulary and in the electronic ordering system. Due to myriad anecdotal accounts of unofficial nonformulary requests, we decided it was important to also have a way to review the indications for and evidence behind specific requests on a case-by-case basis to ensure appropriateness. The ultimate goal of this initiative was to promote evidence-based practice and to minimize waste and resource overutilization while improving patient outcomes.

We began by performing an exhaustive review of the US National Library of Medicine online database for descriptions of similar projects. We used the keywords *chemotherapy*, *antineoplastic*, *hematology*, and *oncology* along with the secondary keywords *stewardship* and *control*, in all potential combinations. This literature search yielded no results focusing on a stewardship program to help guide and encourage the rational use of evidence-based regimens to treat cancer.

The stewardship pilot program took place at Mount Sinai Hospital from June 30, 2014, to June 30, 2015. Although outpatient requests were included as the need arose, the program focused on the inpatient setting because requests were easier to centralize and track and it was felt that such a program would have a larger and more measurable impact in the hospital, where cancer treatment is more expensive. All physicians who requested medications through this program were on faculty at the attached medical school; no private-practice providers were involved. Inclusion criteria were any requests made for nonformulary and/or off-label cancer therapies that were submitted along with supporting evidence. Exclusion criteria included any drugs that were on formulary and being used for approved indications, as well as those that could only be obtained through restricted specialty pharmacies. Our preliminary findings were presented as an abstract at the 2015 Annual Meeting of the Society of Hematologic Oncology in Houston, Texas.¹⁰

A board-certified hematologist-oncologist specializing in hematologic malignancies was designated by the division chair to act as the “steward” and address all requests for use of nonformulary or off-label antineoplastic agents and regimens. All medical staff in the division, including faculty, fellows, and ancillary providers, were directed by the oncology pharmacy to contact the steward by email whenever they attempted to order such medications. The medical team would have to officially submit at least 1 peer-reviewed journal article and their rationale for use to the steward. The steward would then have an academic discussion with the team, as well as with other physicians and pharmacists who made up an informal “stewardship committee,” and then either approve or deny the request. The decision was then communicated via email to supervising oncology pharmacists who would release the drug(s) in question if the request was approved. All requests were collected

TABLE. Details of Cancer Therapy Approval Requests

Diagnosis	Requests (n)	Reasons for Drug Request Per Diagnosis (n)	Approved Medications (n)	US ASP Per Dose (\$)ª
Multiple myeloma	13	Progression (5) Bone therapy (4) Hypercalcemia (2) Stem cell collection (1) Refractory nausea (1)	Denosumab (5)	2350
			Bendamustine (4)	5023
			Zoledronic acid (1)	72
			Carfilzomib (1)	2234
			Plerixafor (1)	8653
			Granisetron (1) [outpatient]	24
Non-Hodgkin lymphoma	11	Progression (10) GVHD (1)	Bendamustine (4)	5023
			Brentuximab (2)	22,000
			Brentuximab and bendamustine (2)	27,023
			Romidepsin (1)	9910
			Pembrolizumab (1)	N/A
			Protopic (1)	500
Amyloidosis	7	Stem cell collection (7)	Plerixafor (7)	8653
Hodgkin lymphoma	7	Progression (7)	Bendamustine (3)	6300
			Bendamustine and brentuximab (3)	28,300
			Nivolumab (1) [outpatient]	5840
Acute myeloid leukemia	6	Progression (1) Nausea (1) Vaginal bleeding (1) aHUS (1) GVHD (1) Exposure to varicella (1)	Sorafenib (1)	288
			Palonosetron (1)	N/A
			Ortho-Evra patch (1)	44
			Eculizumab (1)	22,000-29,000
			Protopic (1)	500
			Varicella immunoglobulin (1)	N/A
Acute lymphoblastic leukemia	3	Progression (3)	Liposomal vincristine (1)	13,635
			Blinatumomab (1)	3814
			Ponatinib (1)	N/A
Immune thrombocytopenic purpura	4	Refractoriness (4)	Eltrombopag (2)	256
			Romiplostim (2)	1818
Aplastic anemia	3	Refractoriness (3)	Eltrombopag (1)	256
			Romiplostim (2)	1818
aHUS	3	Standard of care (3)	Eculizumab (3)	22,000-29,000
Paroxysmal nocturnal hemoglobinuria	1	Admitted for procedure and continued outpatient eculizumab (1)	Eculizumab (1)	22,000-29,000
Other	11	N/A	Mix of requests including lenalidomide, ponatinib, and vorinostat (11)	N/A

aHUS indicates atypical hemolytic-uremic syndrome; ASP, average sales price; GVHD, graft-versus-host disease; N/A, not applicable.
ªCalculated using usual dose for the indication and using a body surface area of 1.7 m² or body weight of 70 kg.

by the steward over the course of the year in an email folder and then reviewed retrospectively to prepare this report.

RESULTS

Over the course of 1 year, 67 requests for nonformulary or off-label antineoplastic agents/regimens were made and reviewed by the

Cancer Therapy Stewardship Program, as detailed in the [Table](#). These requests came from 23 physicians and pertained to 66 patients. Ninety-seven percent of the requests (n = 65) were for inpatients, whereas the remaining 2 requests were for 1 outpatient. The most common context for these requests was progression of disease, which necessitated inpatient stabilization and management. Upon review, these requests tended to fall into 1 of the following

categories: 1) use of a drug in a setting not approved by the FDA (eg, using bendamustine for multiple myeloma), 2) use of multiple drugs in novel combinations not approved by the FDA (eg, combining romidepsin and brentuximab for non-Hodgkin lymphoma), and 3) adding novel drugs to existing FDA-approved regimens (eg, adding daratumumab to a carfilzomib-based regimen for multiple myeloma).

The most commonly approved medication was bendamustine (n = 15), either alone or in combination with brentuximab (n = 6), which was the third most commonly requested medication for inpatients. Plerixafor was approved 8 times for inpatients, primarily for stem cell mobilization in patients with amyloidosis. One patient with T-cell lymphoma had multiple requests; he had received bendamustine during an admission for disease progression, then received brentuximab and romidepsin during a second admission for continued progression of disease. The only outpatient requests were nivolumab and granisetron for a patient with progressive Hodgkin lymphoma and uncontrolled nausea who was intolerant of ondansetron. All requests eventually were approved after going through stewardship review.

DISCUSSION

Our experience with piloting this stewardship program yielded many useful insights. For instance, collecting data on prescribing practices gave our department the ability to systematically review and analyze how our physicians dealt with challenging clinical situations in hematologic oncology. The fact that every request was approved helped demonstrate to department leadership that our physicians are attuned to providing optimal evidence-based care. Furthermore, by focusing on nonformulary or off-label agents and regimens, the program also served to highlight novel and experimental approaches to managing complicated diseases for which standard therapies have failed. The stewardship process facilitated discussions among the treatment teams so that everyone involved could work together to pursue better patient outcomes. By encouraging discussion and collaboration, the program also served to promote evidence-based practice and academic exploration at our institution.

As an example, we learned that bendamustine, the most commonly requested drug during the study period, was used extensively for cases of multiple myeloma that proved refractory to several prior lines of treatment. These requests were submitted along with 1 of any number of recent studies suggesting improved patient outcomes when using this drug in this setting.^{11,12} This eventually led to discussions among division leaders regarding the potential inclusion of this medication in the hospital formulary and in the electronic ordering system in order to streamline workflow and increase efficiency. Another important point that this example raised is that the value of certain agents or regimens will invariably change over time as more is learned about each drug and as

new and improved drugs come out. Since we began this project, bendamustine has been all but replaced by daratumumab for use in relapsed/refractory multiple myeloma, a fact that highlights the need for regular meetings, perhaps on a yearly basis, to formally evaluate and update the formulary based on new research. This example illustrates the many potential roles and benefits such a stewardship program can have in the realms of patient care, medical education and investigation, and quality improvement.

This program also proved to be a useful way to monitor and regulate resource utilization in an effort to help decrease unnecessary spending and contain cost. A key example of this was the use of blinatumomab for patients with relapsed acute lymphoblastic leukemia. Because the average sales price for a 28-day treatment cycle using the FDA-approved dose was \$106,800, this agent helped illustrate the importance of such regulation. After a few requests were made to use this medication in this setting, the steward collaborated with the requesting physicians and the pharmacy department to help develop and introduce a change in the way this medication was dispensed and administered by preparing it as a 48-hour infusion. This change, which led to a decreased cost of administration and helped streamline the treatment process, would not have been as easily achieved if such a program for monitoring and review were not in place.

Limitations

A potential critique of this program is that every request ended up being approved, which may call into question its usefulness. However, based on our observations, we believe that the very existence of this program encouraged our physicians to be especially thoughtful in their requests. Because each request was considered only if it was accompanied by supporting data, a thorough literature search was essentially a prerequisite for submission, and so there was likely an element of selection bias involved. In addition, it is impossible to know which requests were considered for submission but ultimately not pursued due to a low likelihood of approval based on a lack of available supporting evidence, although there were several such anecdotal accounts described over the study period.

The argument could also be made that our results provide sufficient evidence that this pilot program does not need to continue at our institution. Although this realization itself is informative, as it suggests there is little to improve upon, we would argue for its continuation in order to delve deeper into this issue and try to quantify more concrete outcomes in subsequent studies. Importantly, implementation and maintenance of this program was very simple and did not require any additional financial resources to achieve. Because it essentially formalized a process that already takes place when physicians face challenging clinical situations (ie, reviewing the literature and discussing options with colleagues), it did not require anything extra in terms of resources or time. The pilot program has been completed, and we are in discussions regarding

the feasibility of piloting this type of project in the outpatient setting and extending it to other hospitals within our health system.

CONCLUSIONS

Resource utilization review programs, such as our stewardship initiative, will become increasingly important as the concept of value takes center stage in healthcare. Regulatory agencies and governing bodies have begun to implement programs in which institutions are rewarded for increasing overall healthcare quality within the context of value. Indeed, CMS has been exploring the use of bundled payments for episodes of care as a way to increase quality and coordination of care and simultaneously lower costs. A related new CMS initiative, the Oncology Care Model, invites applicant practices to enter into reimbursement arrangements that include financial and performance accountability for episodes of cancer care.¹³ Implementing a cancer therapy stewardship program is 1 way cancer centers can begin to adapt to this new healthcare landscape. Aside from its focus on value-based care, this program helped enhance patient care, medical education, and quality improvement. Although we were not able to specifically measure quantitative outcomes in these areas in this pilot study, we believe that this project has laid the groundwork for subsequent work in each of these important realms. ■

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Source of Funding: None.

Author Disclosures: The authors report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (ASS, SK, LI); acquisition of data (ASS, DP-H, TA); analysis and interpretation of data (ASS, ABP, SK,

TA, LI); drafting of the manuscript (ASS, ABP, SK, LI); critical revision of the manuscript for important intellectual content (ABP, DP-H, TA); statistical analysis (ASS); provision of patients or study materials (DP-H); and administrative, technical, or logistic support (ASS, ABP).

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REFERENCES

1. Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. *J Pediatric Infect Dis Soc*. 2015;4(4):e127-e135. doi: 10.1093/jpids/piu141.
2. Boel J, Andreasen V, Jarlov JO, et al. Impact of antibiotic restriction on resistance levels of *Escherichia coli*: a controlled interrupted time series study of a hospital-wide antibiotic stewardship programme. *J Antimicrob Chemother*. 2016;71(7):2047-2051. doi: 10.1093/jac/dkw055.
3. Trinh TD, Klinker KP. Antimicrobial stewardship in the emergency department. *Infect Dis Ther*. 2015;4(suppl 1):39-50. doi: 10.1007/s40121-015-0084-8.
4. Murri R, de Belvis AG, Fantoni M, et al; Collaborative SPES Group. Impact of antibiotic stewardship on perioperative antimicrobial prophylaxis [published online June 9, 2016]. *Int J Qual Health Care*. doi: 10.1093/intqhc/mzw055.
5. National Healthcare Expenditure Fact Sheet 2014. cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html. Updated August 10, 2016. Accessed August 18, 2016.
6. Mariotto AB, Yabroff R, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst*. 2011;103(2):117-128. doi: 10.1093/jnci/djq495.
7. Pollack A. Cancer doctors offer way to compare medicines, including by cost. *The New York Times*. June 22, 2015. nytimes.com/2015/06/23/business/cancer-doctors-offer-way-to-compare-medicines-including-by-cost.html. Accessed October 9, 2016.
8. Kantarjian HM, Fojo T, Mathisen M, Zwelling LA. Cancer drugs in the United States: justum pretium—the just price. *J Clin Oncol*. 2013;31(28):3600-3604. doi: 10.1200/JCO.2013.49.1845.
9. Schnipper LE, Davidson NE, Wollins DS, et al; American Society of Clinical Oncology. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol*. 2015;33(23):2563-2577. doi: 10.1200/JCO.2015.61.6706.
10. Steinberg A, Peralta-Hernandez D, Kim S, Aggour T. Hematologic oncology chemotherapy stewardship program: a one year institutional experience [SOHO abstract 1003]. *Clin Lymphoma Myeloma Leuk*. 2015;15(S2):S76-S77. clinical-lymphoma-myeloma-leukemia.com/article/S2152-2650(15)00572-8/fulltext. Accessed February 18, 2018.
11. Pozzi S, Gentile M, Sacchi S, et al. Bendamustine, low-dose dexamethasone, and lenalidomide (BdL) for the treatment of patients with relapsed/refractory multiple myeloma confirms very promising results in a phase I/II study. *Leuk Lymphoma*. 2017;58(3):552-559. doi: 10.1080/10428194.2016.1205741.
12. Naymagon L, Abdul-Hay M. Novel agents in the treatment of multiple myeloma: a review about the future. *J Hematol Oncol*. 2016;9(1):52. doi: 10.1186/s13045-016-0282-1.
13. Oncology Care Model. CMS website. innovation.cms.gov/initiatives/Oncology-Care. Updated January 8, 2018. Accessed January 29, 2018.

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