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Identifying Chronic Graft-Vs-Host Disease and Discussing Treatment Options



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At an *Around the Practice*[®] program hosted by CancerNetwork[®], experts spoke about strategies for managing and preventing graft-vs-host-disease (GVHD). The discussion was led by **Yi-Bin Chen, MD**, director of the Hematopoietic Cell Transplant & Cell Therapy Program and the Allen B. Rogers, Jr and Cara J. Rogers Endowed Chair at Massachusetts General Hospital as well as associate professor of medicine at Harvard Medical School in Boston, Massachusetts.

Panelists included **Amin M. Alousi, MD**, professor of medicine in the Department of Stem Cell Transplantation and Cellular Therapy and director of the Multi-Discipline GVHD Clinic and Research Program at The University of Texas MD Anderson Cancer Center in Houston; **Nelson J. Chao, MD, MBA**, cellular therapy and stem cell transplant specialist at Duke Health in Durham, North Carolina; and **Hana Safah, MD**, professor of clinical medicine and director of the Stem Cell Transplantation Program and the Leukemia and Lymphoma Programs at Tulane Cancer Center in New Orleans, Louisiana.

Understanding GVHD

CHEN: How can transplants help patients with cancer, and how does that relate to GVHD?

CHAO: Transplant is the first immunotherapy that we had. It had been around for 45 years or more when it became clear that you could transfer somebody's immune system with bone marrow cells. When we do a bone marrow

transplant, there tend to be 3 components. You must ablate the recipient so there is no rejection, give the stem cells with hematopoiesis, and then, because of hematopoiesis, you replace the immune system. The immune system is a big component of the transplant. You give the preparatory regimen to treat the underlying disease, but the new immune system can cause what we call graft-vs-leukemia or graft-vs-tumor effect, which is recognizing the host tumor as foreign and getting rid of it. Graft-vs-leukemia has a counterpart, which is GVHD. Just as leukemia can be formed in the donor cells, host tissue can be formed in the donor cells as well and causes a disease we call graft-vs-host.

CHEN: What are the different types of hematopoietic stem cells we use, and how has that changed during the past few years?

SAFAH: The easiest way to speak of it is [in terms of] where the stem cells are coming from, the peripheral blood vs the bone marrow. There is also cord [blood], and although adult stem cell transplants [SCT] use it in very few instances, it is more common when it comes to using SCT in the pediatric state.

With each of those stem cells sources and grafts, there are expected complications, especially when we are talking about GVHD and mainly chronic GVHD. Studies and data have shown that with bone marrow stem cells, there is less frequent—and a lower burden of—chronic GVHD on the patients following SCT, as well as better recovery and quality. Having said that, there is no difference [between strategies in terms of] relapse and overall survival. When you look at the donors, you have the match related or the match unrelated; then there is mismatch related and mismatch unrelated. When we talk about mismatch related, we are talking mostly about the haploidentical [transplant], which is becoming [a preferred strategy] in SCT. We have learned so much from doing

haploidentical SCTs, especially when it comes to learning how to take care of GVHD and the effect of treatments being applied. It is being used by us to take care of GVHD in trials as well as in practice when we deal with match unrelated or mismatch unrelated.

CHEN: Are there any data on a specific type of donor that works best?

ALOUSI: Data are evolving, but in terms of algorithms, match-related donors are at the top of that algorithm as the first donor of choice. The reason for that is studies have shown lower rates of GVHD and treatment-related mortality. In some settings, that may not always be the case. There are data to suggest that if a patient has advanced or high-risk disease, that may not apply. There are conflicting data that show the benefits or lack thereof [for differing strategies] if donors are older and have a matched sibling vs a younger age match. There is the analysis that we did several years ago within the [Center for International Blood and Marrow Transplant Research] that showed older matched siblings still do better than unrelated regarding complications in GVHD, treatment-related mortality, and overall mortality. Some recent data suggest that in myelodysplastic syndromes that's still no longer the case. Once you get away from that, there are several analyses that suggest comparable outcomes for a half-match or haploidentical family member donors as match term-related donors. Increasingly, data suggest that even mismatch-related donor outcomes can be comparable provided the right type of GVHD prophylaxis is employed in those strategies.

CHEN: How is prophylaxis being used to mitigate GVHD?

ALOUSI: We convert about 90% to 95% of our patients to use of posttransplant cyclophosphamide on days 3 and 4 in combination with tacrolimus and a short course of mycophenolate mofetil. Apart from patients who have contraindication

or whom we believe to be at high risk for cyclophosphamide-specific issues, that is our sole GVHD prophylaxis regimen.

CHEN: How can you identify GVHD? What is the pathophysiology behind it?

CHAO: We know it's a T-cell-mediated disease, so if you do an extensive T-cell ablation, you don't see it. In that case, you end up with problems of nongraft and relapse if you don't have any T cells. T-cell recognition of allogeneic peptides presented by MHC [major histocompatibility complex results in] much more of an acute inflammatory response, not terribly different from cytokine release-type symptoms where you end up having significant damage to the gut, skin, and liver. We think it's the gut microbiome that drives the donor T-cells to be activated and it might go to the other organs, but it's predominantly a disease of the skin, the gut, and the liver, although we sometimes see [central nervous system] disease or lung disease.

CHEN: How do you approach a patient with chronic GVHD?

SAFAH: There is a big difference between how the patients present with acute compared with chronic GVHD. For those who presented with chronic GVHD, I tell my patients to expect something like an autoimmune disease where symptoms can creep up slowly. We don't have this angry reaction that we see with acute GVHD where the rash is all over and it's angry and red. Here you see some changes in the skin like sclerotic changes, and then that will progress to involvement of the joint with limitation in the range of motion. Some of the patients come in because they cannot do the work they used to do. Usually, [patients] also suffer from weight loss. Whenever they start complaining of weight loss, in my mind it is chronic GVHD. The interesting part is chronic GVHD can mimic anything, so whenever I see a patient who had an SCT in the past and comes in with weird symptoms, I am thinking it's chronic GVHD.

CASE 1

- Patient characteristics:
 - A man aged 44 years underwent myeloablative conditioning with matched unrelated hematopoietic SCT for acute myeloid leukemia with tacrolimus plus methotrexate for GVHD prophylaxis.
 - The donor was a woman aged 48 years who was cytomegalovirus seropositive with 2 children.
- On day 26, the patient developed a maculopapular rash on his face, chest, forearms, shoulders, and back.
 - The estimated body surface area involvement was 60%.
 - The patient also experienced 3 or more episodes of watery diarrhea for 2 days.
- Treatment:
 - He received prednisone, 2 mg/kg/d for 14 days.
- The skin rash was reduced to grade 1 and the diarrhea was resolved.
- The steroid dose was tapered by 10% every 5 to 7 days.

CHEN: What would be your next steps?

ALOUSI: I'm a firm believer that any patient who is early post transplant and presents with diarrhea has GVHD until proven otherwise. I believe this prompts an evaluation and work-up. Generally, that would include admission to the hospital in an expedited fashion with endoscopy and biopsies. Certainly, obtaining stool to rule out [infections] or other medications that may present is part of the evaluation. I do believe diarrhea is a high-risk manifestation of GVHD because we do know that there's a preponderance of lower GI [gastrointestinal] GVHD in the steroid-refractory setting and treating these patients early is important.

CHEN: How do biomarkers play a role in GVHD?

SAFAH: There are certain patients who come in with GI stage 1 adverse effects and skin [rash], and then they do poorly. Clinically, and what I teach my fellows is, you must follow your patients. Within 3 to 5 days, you want to make sure they're not progressing at 5 days and make sure that they're responding. At 7 days, they must respond clinically, and this is going to tell you how they're going to do with the treatment and [whether you must] change treatment accordingly. The biomarkers that I use just to give me an idea of who's going to do well don't change the treatment plans. I use it for prognostication.

ALOUSI: We don't have evidence showing that treating patients differently based on biomarkers is helpful. One caveat is a paper that was pivotal in biomarker and GVHD research called MaGIC [Malignant Germ Cell International Consortium] that looked at biomarkers on day 7.¹ That's an area where the data are interesting. If you look at the traditional definition of who responds to steroids or not, typically patients who progress after 3 days of high-dose [treatment] or who fail to respond by 7 to 10 days are considered steroid refractory. When MaGIC looked on day 7 at the biomarkers of the population who would be characterized as steroid refractory based on that definition, they had very interesting findings. About 50% of the patients who met the definition of steroid refractory returned with a biomarker that suggests they were low risk, and 50% returned with a high-risk phenotype. When they looked at roughly 50% of the patients who would otherwise be characterized as steroid refractory but had a low-risk biomarker, they found that their outcome with respect to GVHD response at day 28 as well as their likelihood of experiencing treatment-related mortality at 6 months was the same as those who were characterized as being responders. That tells us about 50% of the patients may be what I like to call slow responders to steroids but are not truly steroid refractory.

CHEN: How would you respond to a patient with lower GI disease who is receiving steroids and had a partial response [PR] on day 28?

ALOUSI: Look at day 28 response data, patients classified as having a PR did similar to those who had a complete response [CR], but that's not the full story. Mainly those patients had a PR to skin GVHD, not lower GI GVHD. In the databases used to establish the day 28 response criteria, very few patients who were in a PR had lower GI involvement and were characterized as being in a PR. The reason is very few clinicians wait 28 days for somebody's diarrhea to get better before they start second-line therapy. Once you start second-line therapy, that's progressive disease or treatment failure. That population who had a PR on day 28 were like those who had a CR and whose symptoms were limited to some upper GI and skin GVHD, but not those with diarrhea. If a patient is still having diarrhea for an extended period and you're out more than 14 days, even if it's better than where they started, it's uniformly accepted that that patient would ultimately get a second-line therapy. I believe that to be the best practice. In a clinical trial, ruxolitinib [Jakafi] is the only FDA-approved therapy in that setting, but considering a patient for clinical trials is always appropriate when available because we can certainly do better.²

CASE 2

- Patient characteristics:
 - A woman aged 59 years had a postmatched unrelated donor with hematopoietic SCT with peripheral blood stem cells for acute myeloid leukemia with myeloablative conditions with busulfan and cyclophosphamide and GVHD prophylaxis of tacrolimus plus methotrexate.
- At 13 months or more, the patient presented with dry eyes and foreign body sensation. She was given topical agents, but symptoms persisted.
- At 16 months or more, the patient presented with muscle and joint pain that limited daily exercise and routine. She responded to prednisone.
- At 20 months or more, sclerodermatous formed and changes occurred. This decreased the range of motion, forced expiratory volume in 1 second, and diffused capacity of the lung for carbon monoxide on the pulmonary function test without dyspnea.

CHEN: What is the significance of receiving peripheral blood stem cells for chronic GVHD?

CHAO: There's a study [NCT00075816] done by the Blood and Marrow Transplant Clinical Trials Network randomizing patients to bone marrow vs peripheral blood.³ That study showed no difference in the overall outcome, but clearly the rate of chronic GVHD is highest in those who got peripheral blood. The incidence was significantly higher in those patients, so when we use peripheral blood we know the chance of getting chronic GVHD is going to be higher.

CHEN: The data from that study haven't changed practice. How have recent world events influenced where stem cells are sourced from?

ALOUSI: We don't know why it hasn't changed practice. Long-term follow-up results from that trial found much poorer long-term quality of life in those who received peripheral blood vs bone marrow. The likelihood of return to employment was much lower in the group that received peripheral blood than bone marrow. If patients knew the results of that follow-up trial, they would voice their opinion and practice may change. But that information isn't widely disseminated in patient portals and discussion groups, and that hasn't changed practice. It's hard to change a clinician's behavior. Early on, there was some belief that peripheral blood may lower the risk of relapse. When you look at the results of that [study], relapse rates were identical between those 2 arms. There still is a widely disseminated belief that blood

stem cells lower the risk of recurrence.

COVID-19 may have changed practice in that many providers want to get quicker engraftment, and blood stem cells can be quicker than bone marrow. Having the cells here and cryopreserved to get quick recovery is something that clinicians in the middle of a pandemic felt to be important. When cryopreserving bone marrow, there can be some concerns with doing this, although it can certainly be done. Those [may be some reasons] why practice hasn't changed as much as it should have based on what we know about the risk of GVHD in those who get blood stem cells.

SAFAH: It's easier to send a donor for peripheral blood collection compared with getting a donor to have a bone marrow harvest. [You run into issues getting the] bone marrow harvested because transplant physicians are the ones usually in the collection center, so there's no one able to do that and have it done in a timely fashion. The operating room time is so limited and with the limited resources, like nurse availability, [harvesting bone marrow is that much harder].

CHEN: How is chronic GVHD staged?

CHAO: For years we didn't do a very good job. DNA consensus criteria came to be over 10 years ago where each of these potential organ sites which are affected—typically areas like the skin, mouth, eyes, GI tract, lung, liver, that general area—gets scored from 0 to 3 and then we can add these up. This was instrumental to allow different centers to conduct clinical trials using the same language instead of using terms like *limited* or *extensive*. It's

much more of a formal assessment and I think adding performance status makes a big difference as well for that analysis.

ALOUSI: It's very difficult getting every clinician trained on doing a chronic GVHD assessment. Studies have shown that it can be done in as little as 10 to 15 minutes. But getting everyone on board to do it and do it regularly is very challenging. Under-reporting of chronic GVHD occurs if no one's doing the assessment and the patient doesn't [receive a diagnosis of] GVHD.

CHEN: When assessing the patient case, what steroid dosage would you begin with and when do you start second-line therapy?

SAFAH: I would start her on 1 mg/kg of prednisone. I tend not to go very high, and I give it enough time for a response to be documented with chronic GVHD. It also depends on the organ that there is involvement with, especially when it comes to lungs. I don't wait too long with lungs, and I follow the pulmonary function tests quite frequently in these patients. If there is no improvement, I start with 14 days and then 28 days [of treatment].

For the second line, if it is liver, lung, or other organs being involved, this is where I switch to a second-line agent and JAK inhibitors. This is my go-to after 1 line of therapy failure. If a patient continues to not do well or cannot receive JAK inhibitors, then a Rho kinase inhibitor is another option. ■



For references visit
cancernetwork.com/GVHD_10.22