“Part of this is due to the fact that brain tumors have such poor prognosis in general, and any tools to help improve the resection can have immediate short-term benefit on patients’ lives. A substantial benefit for brain tumor patients will probably come in improved systems to track weak fluorescence signals in areas not well resected using current systems, and in tumor subtypes that do not present well with ALA-PpIX fluorescence or vascular marking fluorescence such as fluorescein or indocyanine green.”

Liu said that the combination of the distinctive contrasting agent and the microscopic device sets his group’s research apart. “It’s very important to use the two together,” said Liu. “There are a lot of contrast agents being developed, and there are other types of imaging devices. We took those two worlds and brought them together, showing that by using advanced microscopy technique, you can see the tumor cells and differentiate them from the normal cells with the use of this contrast agent.”

The Stony Brook researchers believe that the combination of intraoperative confocal microscopy with molecularly targeted contrast agents could complement current image-guided surgery approaches, such as those with magnetic resonance imaging or computed tomography, to surgically remove brain tumors and other forms of cancer.

Nader Sanai, M.D., director of the Division of Neurosurgical Oncology and Barrow Brain Tumor Research Center at St. Joseph’s Hospital in Phoenix, said he believes that the study is an important advance. “I think it is a clever way of using the tumor’s molecular biology to tell you where you are at with respect to the margins of the tumor. Plus, your naked eye is only going to tell you so much.”

Sanai said that although microscopes are already in the operating room, they offer only magnification, not cellular resolution. “This device,” he said, “in combination with intelligently selected probes, gives you an entirely different dimension of understanding of what you’re looking at, where the tumor cells are, and how much you’ve actually done in removing them.”

Friedman has a mixed reaction to the research and this study in particular. “Most of the studies published so far do suggest that the completeness of the resection is enhanced by using this technique,” Friedman said. “So that’s the good news. The bad news is that the fluorescence is only on the surface, meaning it’s limited. You can’t see anything that’s going on under the surface, since the light doesn’t penetrate more than a couple of millimeters. This means that no matter how good your resection is, you’re never going to completely cure these tumors with surgery.”

Preventing Graft-Versus-Host Disease: Transplanters Glimpse Hope Beyond Immunosuppressants

By Caroline McNeil

In the early 2000s, sirolimus (Rapamune) looked promising to prevent graft-versus-host disease (GVHD) in leukemia patients with bone marrow transplants. More than a decade later, a Dana–Farber Cancer Institute researcher stood before the December 2012 meeting of the American Society of Hematology with disappointing news: In phase III trials, the drug proved no better than placebo.

Corey Cutler, M.D., and colleagues were hardly the first to face the problem of GVHD. Ever since hematopoietic stem cell transplants emerged as a lifesaving treatment for leukemia and other hematologic diseases 40 years ago, patients and physicians have had to balance its benefits against serious risks.

Transplants restore stem cells destroyed by high doses of chemotherapy and/or total-body irradiation (TBI), the conditioning regimens that prepare patients for infusions of cancer-free, and cancer-fighting, stem cells. GVHD, which develops when donor T cells attack patient cells they see as foreign, is a life-threatening condition affecting the skin, liver, intestines, and other organs. The mortality rate for chronic GVHD is 40%.

GVHD also profoundly affects quality of life. “It completely interrupts normal life,” said Susanne Liewer, Pharm.D., pharmacy coordinator at the University of Nebraska’s Blood and Marrow Transplant Service.

The longstanding preventive agents are immunosuppressive drugs—cyclosporine, tacrolimus, and methotrexate—given immediately after transplant. Despite these, 60% of patients still develop acute GVHD in the first 100 days, and up to half develop chronic disease. The rates have changed little for decades.

But last year brought news of successful trials with new drugs and other approaches to prevention. In February, at the combined meetings of the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research—the large, annual tandem meetings of the transplant world—speakers highlighted strategies for trials that go beyond immunosuppression.
Prevention Pipeline

One of the highest-profile drugs in the running is maraviroc (Selzentry), a CCR5 antagonist and HIV drug that prevents T cells—the chief culprits in GVHD—from moving into vulnerable organs. In a randomized phase I/II trial published last July in the New England Journal of Medicine, maraviroc plus tacrolimus reduced the incidence of GVHD in the liver and gut without compromising the immune system.

However, risk increased after 6 months with the occurrence of late, acute GVHD. The researchers, at the University of Pennsylvania's Abramson Cancer Center, now plan to try a longer regimen with maraviroc to prolong its benefit.

- Four other drugs with different mechanisms of action also emerged from recent early-phase trials: Bortezomib (Velcade), a proteasome inhibitor, reduced acute GVHD to 22% and chronic GVHD to 29% in a phase I/II trial at Dana–Farber. Amin Alousi, M.D., of the University of Texas M. D. Anderson Cancer Center in Houston, reviewed the state of GVHD research at the tandem meetings and said these rates were impressive.
- Pentostatin, a nucleoside inhibitor, combined with standard prophylaxis, resulted in grade III–IV acute GVHD in just 10.7% of patients in a randomized trial at M. D. Anderson.
- Vorinostat, a histone deacetylase inhibitor, combined with standard medications, resulted in just 21% of patients' developing grade I–II GVHD in a proof-of-concept trial at the University of Michigan and Washington University in St. Louis.
- Posttransplant cyclophosphamide, which depletes alloreactive T cells, has had promising results. In combination with standard prophylactic drugs, it demonstrated a 34% incidence of grade II–IV acute GVHD and a 5% incidence of chronic GVHD in an M. D. Anderson study.

Another prevention strategy, T-cell depletion (TCD), which rids a transplant of alloreactive T cells, ex vivo or in vitro, has been under study for years and continues to be refined. Researchers at the Center for International Blood and Marrow Transplant Research, Dana–Farber, and other centers recently showed that using CD34+-selected T cells produced lower rates of chronic GVHD than did a standard prophylactic regimen (19% vs. 50%). Unlike earlier TCD trials, no statistically significant differences in treatment-related survival were evident.

Transplantation Factors

Meanwhile, clinicians have one new, non-drug, non-TCD approach to try. Patients contemplating transplants have several risk factors to consider: They might receive stem cells from peripheral blood or bone marrow, have reduced-intensity conditioning or myeloablative conditioning, and receive TBI as part of the conditioning regimen or not. Two recent studies suggest that these modifiable risk factors can make a statistically significant difference in GVHD rates without affecting survival.

In a phase III trial led by Claudio Anasetti, M.D., at the H. Lee Moffitt Cancer Center and Research Institute in Orlando, Fla., GVHD rates were lower among patients who received bone marrow transplants than in those who received peripheral blood stem cells. That finding confirmed the results of smaller studies, with the difference that, in this large randomized trial, relapse rates and overall survival were similar in both groups.

Published in the New England Journal of Medicine in October, the trial was the first of its kind in unrelated, matched donors, which now account for 76% of transplants. The authors conclude that peripheral blood transplants might be used in patients at higher risk of graft failure, which is less common with peripheral blood, but that “bone marrow transplants should be offered to all others.”

The results should change practice, according to Frederick Appelbaum, M.D., at the Fred Hutchinson Cancer Research Center in Seattle. But, he added in his editorial accompanying the study, “it will be interesting to see whether it really does.”

That’s because peripheral blood transplants have a key perceived advantage over bone marrow. “It is a donor issue,” said Madan Jagasia, M.D., director of the outpatient transplant program at Vanderbilt–Ingram Cancer Center in Nashville. Donating bone marrow requires general anesthesia and a longer recovery for the donor, some of it in the hospital. Peripheral blood stem cells are harvested in an outpatient setting, using apheresis.

Jagasia was principal investigator of a large retrospective study that also focused on transplantation factors. The 5,000-patient study looked at six treatment variables in different combinations, or “packages,” in both related and unrelated donors.

One package combined myeloablative chemotherapy with TBI and a bone marrow transplant. A second package left out TBI, and a third substituted peripheral blood for bone marrow.

Certain packages reduced GVHD risk. For instance, in unrelated matched donors, those who had a combination of myeloablative conditioning and bone marrow transplants, with or without TBI, had reduced GVHD rates. In most “winning” categories, the source of stem cells was bone marrow rather than peripheral blood. However, rates were lower in patients receiving reduced-intensity conditioning and peripheral blood transplants.

In an editorial accompanying the retrospective study, published in Blood in January 2012, Georgia Vogelsang, M.D., of Johns Hopkins noted that transplant patients used to have just one option: “acceptance of the risk and prayer for a good outcome.” Now, she wrote, “modifying transplantation factors, in addition to prayer, should be considered in deciding on a [prevention] strategy.”

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