

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Is Reduced-intensity Conditioning the Standard of Care in the Transplant Setting?

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### **H&O** How did the paradigm of reduced-intensity conditioning develop?

**SG** Historically, it has been 20 years since the seminal report that patients with refractory acute leukemia could be cured with high-dose radiotherapy plus bone marrow transplanted from a human leukocyte antigen (HLA)-identical sibling. The initial bone marrow transplants were described in the 1950s; of the first 300, only four were successful. At the time, there was little or no knowledge about HLA typing, viruses, graft-versus-host disease (GVHD) or its prevention, and the available antibiotic therapies were limited. Between the 1950s and 1975, many advances occurred that made successful transplantation more feasible. The most important advances were the understanding of HLA typing and improvements in supportive care. From 1975 to 1995, the accepted wisdom was that transplantation is effective because patients receive high-dose chemotherapy and radiotherapy, which kill the resistant cells. The graft then has the primary effect of rescuing the body from the high-dose cytotoxic therapy. Although it was known that the engrafted cells had a potential of conferring an antitumor effect, its importance and the strength of this effect was not elucidated and made evident until 1990 or so when researchers found that patients who relapsed after transplantation could re-enter remission with an additional transplant of hematopoietic stem cells. This transfusion, sans che-

motherapy, would lead to remission in some (though not all) patients. Thus, it was demonstrated that the cells themselves were important in achieving long-term disease control. After it was shown that high-dose chemotherapy was not solely responsible for inducing remission, the paradigm changed. The dogma stated that the only patients eligible for this highly toxic, intensive therapy were young, healthy individuals. However, most patients with leukemia, lymphoma, or myeloma are not young or otherwise healthy. Thus, the patients who would benefit the most from this therapy were generally not offered it because of age and comorbidities. With the realization that high-dose chemotherapy was not the sole cause of remission in transplanted patients, the community began to think about offering transplantation to those who need it the most (ie, elderly and debilitated patients).

To begin researching nonmyeloablative or reduced-intensity conditioning, we observed that a patient who received nonirradiated white-cell transfusion actually experienced donor-cell engraftment. Therefore, it was understood that fludarabine alone could enable engraftment. Thus, fludarabine was combined with lower doses of compounds that are otherwise normally used to treat the malignancy. In some cases, in research in the late 1990s, the conditioning regimen offered was the same as the regimen used in our leukemia trials, with the transplantation of donor cells as the only difference. Using these regimens, donor cell engraftment was observed. Upon examination, the bone marrow was primarily or even 100% composed of donor cells. If these patients remained in remission, that outcome could be attributed to the transplant rather than the chemotherapy, which was not highly cytotoxic. Highly toxic and lengthy chemotherapeutic regimens are associated with tissue damage, which, in turn, leads to GVHD. The ability to use less toxic chemotherapy

and still achieve engraftment allowed older patients to become candidates for transplantation, with lower rates of GVHD.

### **H&O** What were the criteria for identifying reduced-intensity conditioning regimens?

**SG** Initially, the criteria for reduced-intensity regimens were somewhat arbitrary but they were derived from practical experience and observations. For a regimen to be considered nonmyeloablative, it should be possible to administer it without stem cell support. When given without stem cell support, rapid recovery within 3–4 weeks should occur, with no or minimal toxicities. And, donor-cell engraftment, of course, should result, with mixed chimerism. The operational definition of reduced-intensity conditioning was developed in order to compare data from retrospective databases and registries. The definition was: busulfan less than 9 mg/kg, melphalan less than 140 mg/m<sup>2</sup>, less than 500 cGy total body irradiation, and the use of a purine analog.

### **H&O** Which patients are today receiving reduced-intensity conditioning regimens?

**SG** At present, older patients with acute leukemia and myelodysplastic syndromes (MDS) compose a group in whom the use of reduced-intensity conditioning is increasing. Also, patients with indolent lymphoid malignancies such as chronic lymphocytic leukemia (CLL), low-grade lymphomas, and myeloma are also increasingly being given these conditioning regimens. The reason for administering reduced-intensity conditioning is that, though there are no randomized trials to demonstrate its superiority, most clinicians believe transplantation is most successful with this type of regimen. Based on data from clinical-trial registries, patients with acute leukemia, CLL, or an indolent lymphoid malignancy in their fifth and sixth decade of life are most likely to receive reduced-intensity conditioning. Now, older patients with acute leukemia, who have matched donors, are increasingly being offered transplantation because the results appear more promising than those conferred by any other available therapy.

### **H&O** Is there a relationship between the risk of GVHD and the type of conditioning regimen administered?

**SG** The risk of GVHD is probably the same with reduced-intensity conditioning as with traditional, ablative conditioning regimens. If a reduced-intensity regimen containing alemtuzumab (Campath, Genzyme/Bayer) is

used, the risk of GVHD is very low even though the risk of relapse or infection may be high comparatively. Alemtuzumab depletes T cells, which cause GVHD. Research has been undertaken into the use of agents that target B cells, such as rituximab (Rituxan, Genentech/Biogen Idec), in conditioning regimens in lymphoid malignancies. Whether rituximab will have a role in the control or prevention of GVHD has yet to be determined, with studies in this regard currently ongoing.

### **H&O** What avenues of research are currently open regarding reduced-intensity conditioning?

**SG** There is a good deal of research attempting to optimize treatment insofar as which patients should receive reduced-intensity conditioning, how it should be administered, and which combination of drugs is superior. At this point, the optimized treatment has yet to be determined. Further research is investigating the use of new drugs in the transplant setting, either as maintenance therapy (eg, decitabine [Dacogen, MGI Pharma]) or as part of the conditioning regimen (eg, clofarabine). Finally, researchers are beginning to assess which patients are or are not benefiting from reduced-intensity conditioning, with the goal of better patient selection. Are there criteria to use so that patient selection is less arbitrary? Researchers are evaluating the importance of comorbidities as well as surrogate markers such as bone morphogenetic protein, C-reactive protein, immunoglobulin V status, and ferritin. Researchers are also going to begin using the batteries of tests used by geriatricians to evaluate candidacy for transplantation and conditioning regimens as well as considering the importance of gene polymorphisms; the accumulation of large datasets of polymorphisms will help clinicians better understand how to choose patients. At present, however, polymorphisms are not used in the clinical decision-making process in the transplant setting. Busulfan pharmacology is an indirect measure of polymorphism used to modify intravenous doses of busulfan, but there are no specific genetic markers used to predict what doses should be used, for example.

### **H&O** What is the overall status of the decision-making process for clinicians in the transplant setting vis-à-vis conditioning regimens?

**SG** Currently, I believe patients who would be cured by allogeneic transplantation with an ablative conditioning regimen and who are young and relatively healthy should receive that therapy. Older patients who are weak or frail, with impaired liver and/or kidney function, who cannot tolerate ablative conditioning are the best candidates for reduced-intensity conditioning because it would not be

possible to achieve engraftment otherwise. It is expected that outcomes in elderly patients will not be as positive as outcomes in younger patients, but whether the outcomes can be linked to the intensity of the conditioning regimen or the patients' overall health status is unknown. Debate exists as to whether the relapse rate is the same with reduced- versus normal-intensity conditioning. I believe that in many cases the relapse rate is disease-specific, related to the graft-versus-tumor effect, not to the conditioning. In acute leukemias, though, the conditioning dosage is important and is probably related to the relapse rate. Overall, the availability of reduced-intensity conditioning has made transplantation, and its curative potential, available to patients who would not have been considered candidates for this therapy even 10 years ago. Reduced-intensity conditioning may be superior to ablative conditioning in some subsets of patients who have yet to be identified. At present, reduced-intensity conditioning should not be considered a broad-based standard of care because variables related to the type of malignancy,

patient age, and comorbidities must be taken into account. But it is clear that its use is conferring positive outcomes in patients who otherwise would have had a poor prognosis.

### Suggested Readings

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