Neurologic Complications of Bone Marrow and Stem-cell Transplantation in Patients with Cancer

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Current Treatment Options in Neurology 2007, 9:308–314
Current Medicine Group LLC ISSN 1092-8480
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Opinion statement

Transplantation of bone marrow or peripheral blood stem cells is increasingly being used to treat a variety of oncologic disorders. These procedures are associated with a large spectrum of neurologic complications that significantly contribute to patient morbidity and mortality. These complications may arise at any time during and after the transplantation process and are particularly common in patients requiring chronic immunosuppression. The most frequent complications are infections and cerebrovascular or metabolic events, and toxicity from radiation or chemotherapy. Because of the unique circumstances and treatments involved in each step of the transplantation process, there is a higher incidence of some neurologic complications during discrete time periods, and an awareness of the temporal relationship of the neurologic disorder to the transplantation process facilitates diagnosis. With the exception of post-transplant lymphoproliferative disorder, in which reduced immunosuppression may be an effective therapeutic strategy, therapies are often the same as in the nontransplant patient. Complications of therapy can arise because of the presence of multiple comorbidities and medication interactions. Anticipation of common opportunistic infections and appropriate use of prophylactic medications can significantly reduce the incidence of infectious complications.

Introduction

Neurologic complications represent an emerging cause of transplant-related toxicity and pose an obstacle to the success of the procedure. The reported incidence of neurologic complications associated with bone marrow or peripheral blood transplantation (both further referred to as hematopoietic cell transplantation [HCT]) varies based on what is defined as a complication and the population examined. A prospective study of 180 autopsies of HCT patients (177 allogeneic) found neuropathologic abnormalities in more than 90% of the cases [1, Class II], including subarachnoid and intraparenchymal hemorrhages (32% and 27%, respectively), and fungal infections (9%). Studies of clinically symptomatic neurologic complications generally report an incidence of 10% to 40%.

Although it is generally thought that subjects receiving allogeneic cell transplants have a higher risk of developing neurologic complications compared with autologous HCT subjects [2,3], this was not supported by a large retrospective study [4]. This demonstrated that although the incidence of neurologic complications was similar in autologous and allogeneic HCT, the frequency and type of complications varied. For example, subdural hematomas were much more common in patients receiving an autologous HCT for acute myelogenous leukemia (related to refractory thrombocytopenia), whereas...
central nervous system (CNS) infections were more frequent in allogeneic HCT (related to prolonged immunosuppression). Factors that appear to increase the risk of developing an HCT-related neurologic complication include the development of severe acute graft-versus-host disease (GvHD), the use of total body irradiation in the conditioning regimen or pretransplant chemotherapy including intrathecal methotrexate, and prolonged immunosuppression [5, Class II; 6,7]. Each stage of the HCT process (stem cell harvesting, conditioning, period of pancytopenia, period of marrow reconstitution, and long-term immunosuppression) is associated with specific neurologic complications and toxicities. These complications may often be seen throughout the transplantation process and may include drug-induced neurotoxicity, CNS infections, coagulopathies, vascular events, or less commonly, post-transplant lymphoproliferative disorder (PTLD).

## Treatment

### Drug-induced neurotoxicity

- Patients with an underlying autoimmune disease such as multiple sclerosis, rheumatoid arthritis, and chronic inflammatory demyelinating polyneuropathy, among others, may experience an exacerbation of their autoimmune disease while receiving hematopoietic growth factors, in particular recombinant human granulocyte colony-stimulating factor, before apheresis [8, Class III; 9]. The concurrent use of cyclophosphamide appears to decrease the risk of disease exacerbation [8, Class III].

- The high-dose chemotherapy used for conditioning is the cause of most neurologic complications during the period of myeloablation. Chemotherapy regimens vary based on the underlying disease and the source of the stem cells, and each agent can produce acute and in some cases late-onset neurologic dysfunction (Table 1). Seizures occur in approximately 10% of patients administered busulfan, and the prophylactic use of anticonvulsants is recommended [10]. Ifosfamide can cause an encephalopathy in 10% to 40% of patients that is associated with somnolence, confusion, and seizures. Intravenous diazepam and methylene blue have been reported as effective [11, Class III]. The recent use of lower-dose nonmyeloablative regimens and reduced-intensity stem cell transplantation will likely be associated with decreased neurotoxicity [12].

- Corticosteroids are often used throughout the transplant process and are associated with a variety of neurologic complications. A review of HCT patients treated with steroids for acute GvHD found that 41% developed a myopathy that was considered moderately severe in most, with 3% of patients developing a debilitating myopathy [13•, Class II]. The onset of the myopathy is variable but can occur as early as 2 to 3 weeks after institution of therapy. The myopathy is subacute and painless with large thigh muscles most involved, making ambulation difficult [14]; rarely, respiratory muscles can be involved. Discontinuation of the steroids usually is associated with improvement, which can take months. Steroid withdrawal syndrome includes myalgias, arthralgias, headache, lethargy, and nausea with or without a low-grade fever. This syndrome is more likely to occur in patients who have taken corticosteroids for more than 2 weeks and usually follows a rapid taper in dose. In the absence of set guidelines for tapering, decreasing the dosage by 25% every 4 to 5 days is a reasonable approach.

- Cyclosporine and tacrolimus are administered to patients receiving allogeneic HCT as prophylaxis against GvHD, and both cause similar neurotoxicities [15]. A review of 625 patients receiving HCT for thalassemia with cyclosporine demonstrated neurologic toxicity in 28.8% [16, Class II]. The most common side effects were mental status changes, tremor, headache, visual disturbances, and seizures. Most toxicities required no treatment and resolved with dose reduction or discontinuation.