Immunization for bone marrow transplant recipients

B Lynn Johnston MD[1], John M Conly MD[2]

In a previous issue of the journal, we reviewed immunization in healthy, immunocompetent adults (1). In the present issue, we consider immunization in adults who have undergone bone marrow transplants. Bone marrow transplantation (BMT) has become a common procedure for the treatment of several types of hematological malignancies, aplastic anemia and several congenital deficiencies of the bone marrow and immune systems (2). By virtue of the pretransplant preparatory regimens, a temporary state of combined immunodeficiency occurs in all patients after transplantation, with functional recovery of humoral and cell mediated immunity potentially taking a year or longer to develop (2). Multiple components of the host protective mechanisms are impaired, including mucosal barriers, granulocytes, natural killer cells, T cells and B cells (3). Part of the immunodeficiency includes loss of the immune memory that has accumulated over many years of exposure to infectious agents and vaccines (4). While there are some data to support the transfer of memory B cells from donor to recipient, most B cells in BMT survivors have probably developed from bone marrow stem cells, which need to be stimulated to provide long term protection (3). The immunodeficient state is further modified by the use of immunosuppressive therapies, the occurrence of graft-versus-host disease (GVHD) and infection with cytomegalovirus. This immunodeficient state puts the hematopoietic stem cell recipient at increased risk for infection with a variety of pathogens, some of which are preventable by vaccine. An understanding of the level of immune responsiveness after BMT is important, not only for recognizing the risk for infection, but also for determining the optimal timing for vaccine delivery.

POST-BMT IMMUNITY AGAINST VACCINE PREVENTABLE INFECTIONS

Post-BMT antibody levels and in vitro cell mediated immune responsiveness to a variety of bacterial and viral pathogens have been studied in a number of patients, largely in the context of small, post-BMT vaccine studies. Most studies have determined that antibody levels fall after BMT and continue to fall over a number of years, despite reconstitution of the immune system. The roles of transplant source (allogeneic compared with autologous), GVHD (acute and chronic) and natural versus vaccine-induced immunity in the loss of antibody after BMT have not been completely elucidated.

In the 1980s, Ljungman et al (5) found that 77% of 48 allogeneic BMT patients and 71% of their donors were seropositive for tetanus toxoid (TT) before BMT. One year after BMT, only half of the previously immune and none of the nonimmune patients had detectable antibodies. At two years, none of the nonvaccinated patients was seropositive (5). Of note was a positive correlation between the patients' antibody levels before transplant and one year after transplant, raising the possibility of a role for immunization of patients before BMT to improve protection after BMT (5). The authors did not find that tetanus immunity was transferred to seronegative patients from their seropositive donors, but the study involved a small number of patients (5). This fall in antitetanus antibodies has been confirmed by other investigators in both allogeneic and autologous BMT patients (6-8), and one investigator also examined and found a positive correlation between pretransplant and post-transplant antibody levels (6).

Similar falls in protective antibody levels have been observed for poliovirus; diphtheria; measles, mumps, rubella (MMR); and *Haemophilus influenzae* type b (Hib). In one study, none of the seven evaluable patients had protective antibody levels against all poliovirus types one year after allogeneic BMT, although 82% had immunity before transplant (9). For diphtheria, six of 11 (55%) had immunity at one year, compared with 64% before transplant (9). All patients with protective antibodies one year later had been immune before their BMTs and received marrow from a seropositive donor. While another study found that 67% of 55 patients had immunity to all poliovirus types one year after allogeneic BMT, approximately half of the seropositive patients had at least a four-fold decrease in antibody levels during that time (10). Two seronegative patients who had seropositive donors seroconverted in the year after BMT, but their long term protection in the absence of post-BMT immunization was not evaluated (10). As noted previously, while donor B cells may provide early immune memory, it is not considered to be of long duration (9,10). For autologous BMT patients, Pauksen et al (11) found that a similar percentage lost immunity to poliovirus at one year, as did allogeneic recipients. Beyond that time, however, there were fewer who lost antibodies, suggesting that patients are more likely to have residual memory cells after autologous BMT than after allogeneic BMT (11). The presence of acute GVHD was associated with a greater decrease in protective antibody against poliovirus in one study, but could not be demonstrated for chronic GVHD (12).

In two studies, only 6% to 16% of adults had antibody levels that would be considered protective against Hib six months after BMT, compared with 27% to 59% before BMT (9,13). In a cohort (57 patients) of primarily paediatric, allogeneic BMT recipients, among those who were seropositive at the time of transplant, 51% had retained antibodies to measles, 42% to mumps and 76% to rubella two years later, with no differences noted according to type of pretransplant immunity (vaccine versus natural infection) or GVHD (14). On the other hand, another study found that almost 50% of children (nine of 19) but only 2% of adults (one of 44) became seronegative to measles after BMT (15). The study also found that a significantly higher proportion of patients who had vaccine-induced immunity became seronegative than did patients with natural immunity (15). This suggests that natural immunity is more robust than vaccine-induced immunity.

POST-BMT VACCINATION

In view of the studies demonstrating loss of protective antibodies in patients who have undergone BMT, a number of investigators have examined responses to immunization in this group of patients. Most studies were nonrandomized, included small numbers of patients and utilized different immunization schedules. It is, therefore, difficult to make comparisons between different regimens and patient groups. Furthermore, due to the rarity of most of these infections in adults, outcomes in terms of occurrence of

infection have not been evaluable. However, with the exception of pneumococcal immunization, responses to vaccines in patients after BMT are generally good. Receiving more than one vaccine dose has been consistently associated with a better antibody response, in support of the theory that B cell immunity derives largely from donor marrow stem cells rather than memory cells (5,10-12,16-19). There is little evidence to support one dosing schedule over another (6,7,12,13,16,17). For tetanus and polio vaccines, there have been no differences noted between those with and without GVHD in terms of response rate (5,6), although those without GVHD tend to have higher antibody levels (6,12). Likewise, there is no apparent difference between autologous and allogeneic BMT recipients in response to vaccine (19) and between those who receive peripheral blood stem cells rather than bone marrow (20). On the other hand, acute and chronic GVHD did have an impact on response to pneumococcal polysaccharide vaccine, a poor immunogen (13), as did early vaccination after transplantation and corticosteroid therapy (21). Although involving small numbers of patients, none of the studies reported serious adverse events associated with immunization and most did not even comment on the frequency of minor reactions (Table 1).

Improving the response of patients to immunization after BMT is clearly a goal for these patients. A positive association between pretransplantation and post-transplantation antibody levels has already been noted. Although findings have not been replicated by all investigators, some have found that donor antibody status is associated with the response to vaccine, suggesting at least the short term adoption of memory cells from the donor (6,13). This observation is in keeping with an early study demonstrating that B cells synthesizing antibodies against diphtheria and TT could be transferred to BMT recipients by immunizing donors before marrow harvest (22). Immunizing recipients and/or donors before BMT has been explored as a method of improving response to vaccination. In a study comparing 12 patients immunized with Hib-conjugate, TT and pneumococcal polysaccharide vaccines before bone marrow harvest to 41 nonimmunized recipients, there was a trend to higher response rate and antibody levels to Hib and TT, but not against *Streptococcus pneumoniae* (23). In a similar study, allogeneic BMT recipients were allocated to one of two groups where the donor was or was not immunized before bone marrow harvest. Patients whose donors were immunized with Hib-conjugate vaccine and TT had higher antibody levels after transplantation and immunization than did patients with unimmunized donors (24). The authors suggested that recipient and/or donor immunization before bone marrow harvest and transplantation may be a strategy to prevent these and other infections in BMT patients (23,24).

Immunization with an investigational inactivated varicella vaccine has been examined for its ability to reduce morbidity due to varicella-zoster reactivation after BMT. In a study comparing single and three-dose regimens (begin-

TABLE 1
Immunization trials of patients who have undergone bone marrow transplant (BMT)

Country (ref), year	Patient population (n)	Vaccine	Schedule	Response	Adverse events
Sweden (5), 1982-1986	Allogeneic (48)	TT	1-3 doses beginning at 12 months	Higher response rate (100%) and levels in those receiving 3 doses	One severe local reaction
Finland (6), 1985-1989	Allogeneic (45)	TT	gp1: 6, 8, 14 months, gp2: 18, 20, 26 months	Antibody response similar for both schedules (100%)	None noted
Sweden (7)	Autologous marrow (52) or blood (38)	TT	12, 13 and 14 or 18 months	100% response in both patient groups	None noted
Sweden (10), 1982-1987	Allogeneic (55)	IPV	1-3 doses beginning at 12 months	Higher response (92%) rate in those receiving >1 dose	Few minor local reactions
Sweden (11), 1985-1991	Autologous (35)	IPV	12,13,14 months	Antibody levels higher after 3 doses	None noted
Finland (12), 1985-1989	Allogeneic (45)	IPV	gp1: 6, 8, 14 months gp2: 18, 20, 26 months	Antibody responses similar for both schedules (100%)	None noted
Israel (16)	Allogeneic and autologous (27)	IPV	2 doses 4-6 weeks apart 6-96 months	Nonstatistically significant increase in % with antibodies	None noted
Finland (13), 1985-1989	Allogeneic (45)	Hib-con Pn	gp1:Hib 6 mos and Pn 8 months gp2:Hib 18 mos and Pn 20 months	Similar response (approximately 60%) to Hib in both groups. Poor response to Pn in both groups	None noted
United States (17), 1990-1993	Allogeneic and autologous (112)	Hib-con, TT	gp1: 3, 6, 12, 24 months gp2: 6,12, 24 months gp3: 12, 24 months	Similar responses 2 years after immunization in all groups	None noted
United States (19), 1988-1990	Allogeneic and autologous (35)	Hib-con Pn, TT	gp1: 12, 24 months gp2: 24 months	Higher antibody levels to TT and Hib in 2 dose group. Poor response to Pn	None noted
France (18)	Allogeneic (40)	Hib vs Hib-con	Two doses 1 month apart 4-79 months	Better response (85% vs 60%) in Hib-con	No serious
United States (21)	Allogeneic (39)	Pn	1 dose 4-54 months	Small rise in antibody levels post vaccine but less than normal controls	None noted
Sweden (14), 1977-1985	Allogeneic (20)	MMR	1 dose 2 or 3 years	Response rate: measles 77% mumps 64%, rubella 75%	None

Gp Group; Hib Haemophilus influenzae *type b polysaccharide vaccine; Hib-con* Haemophilus influenzae *type b conjugate vaccine; IPV Inactivated poliovirus vaccine; MMR Measles, mumps, rubella vaccine; Pn Pneumococcal polysaccharide vaccine; TT Tetanus toxoid*

ning one month after BMT) to unvaccinated controls, the three-dose regimen was associated with less severe zoster (25). Patients who received the three-dose regimen also had earlier recovery of T cell responsiveness to varicella zoster antigen than did nonimmunized controls (25). Employing the concept that pre-BMT immunization may enhance overall vaccine response, a four-dose inactivated varicella-zoster virus vaccine regimen was studied in lymphoma patients after autologous BMT. The first dose of vaccine was given two to 34 days before BMT. In contrast to the earlier study, there were no differences in severity of zoster between immunized and nonimmunized patients, but there was less zoster (13% versus 33%, P=0.01) in the vaccine group than in the control group (26). Vaccine recipients also had earlier reconstitution of T cell response to

varicella-zoster antigen than did the controls (26). This raises promise that immunization may be effective in accelerating the recovery of cellular immunity to other herpes viruses, including cytomegalovirus (26).

RECOMMENDATIONS FOR VACCINATION AFTER BMT

The recent update of the Canadian Immunization Guidelines (27) has a section dealing with immunization in immunocompromised patients, including BMT patients. The authors acknowledge that while there is a good theoretical basis for providing immunization, there are no conclusive data to support the best schedule, the need for boosters, efficacy in disease reduction or cost benefit. Diphtheria and TT, inactivated poliovirus, Hib, influenza

TABLE 2
Centers for Disease Control and Prevention recommendations for immunization in hematopoietic stem cell transplant recipients

Vaccine	Schedule
23-valent pneumococcal polysaccharide	12 and 24 months
Haemophilus influenzae type b conjugate	12, 14 and 24 months
Varicella zoster virus	Contraindicated
Influenza	Yearly lifelong resuming six months after hematopoietic stem cell transplant
Tetanus-diphtheria toxoid	12,14 and 24 months
Inactivated polio	12,14 and 24 months
Hepatitis B	12,14 and 24 months
Hepatitis A	Routine administration not recommended
Meningococcal	Routine administration not recommended
Measles, mumps, rubella	24 months if immunocompetent

Data from reference 4. Hematopoietic stem cell transplant (HSCT) recipients are considered immunocompetent at 24 months after HSCT if they are not on immunosuppressive therapy and do not have graft-versus-host-disease

and pneumococcal vaccines are recommended routinely after BMT (27). No specific dosing schedules are given. Meningococcal and hepatitis A vaccines are recommended if indicated, and hepatitis B vaccine as per routine use, while MMR, varicella and yellow fever vaccines may be considered at 24 months if there is no immunosuppressive therapy or disease (27). Oral polio, typhoid and cholera vaccines, as well as Bacille Calmette-Guerin are contraindicated (27). The United States Eastern Oncology Cooperative Group indicated in 1994 that it is probably reasonable to consider a number of vaccines at the end of one year without making any clear recommendations (2). In their 2000 guidelines for hematopoietic stem cell transplant recipients (Table 2), the United States Centers for Disease Control and Prevention (CDC) recommended a number of vaccines and offered immunization schedules

(4). The CDC and Canadian guidelines are similar except that the CDC recommends that varicella-zoster vaccine use, even in those presumed to be immunocompetent, be restricted to the research setting until further information is available (4). The European Group for Blood and Marrow Transplantation recommends in its updated guidelines that all BMT patients receive TT, diphtheria toxoid, inactivated poliovirus, pneumococcal, *H influenzae* and influenza vaccines (28). Measles and rubella immunization is considered an individual recommendation based on risk and benefit assessment with vaccination not to be given before 24 months in allogeneic recipients (28).

As with routine immunization in adults, immunization practices following bone marrow transplant may fall short of recommendations. In a 1995 survey of BMT centres in the United States, 88% of the centres provided diphtheria and TT vaccines and 73% provided inactivated poliovirus vaccine following allogeneic BMT (29). Eighty per cent of the centres offered pneumococcal vaccine and 58% offered Hib conjugate vaccine (29). On the other hand, fewer than 50% of programs gave two or more doses, and there were a number of different schedules reported (29). The situation may be improving. In a 1995 survey of the European Group for Blood and Marrow Transplantation centres, 69% and 37% of the centres reported that they routinely immunized recipients of allogeneic and autologous BMTs, respectively (30). As a result of these findings, recommendations for immunization after BMT were published (30). By 1998, 95% of centres reimmunized patients against tetanus, diphtheria and poliovirus (28). Most centres used a multidose schedule, and the majority initiated immunization at least one year from allogeneic BMT (30). Similar data are not available for Canada.

While there are exceedingly few randomized controlled trials of immunization after BMT, there is a good theoretical basis for its use. Many patients will lose immunity to vaccine-preventable infections over time following BMT. Small studies have demonstrated that for most of these infections, most BMT patients will mount an immune response with vaccination. Serious adverse events due to immunization have not been noted. Recent guidelines have been published by both the CDC and National Advisory Committee on Immunization. Physicians looking after BMT patients should review their own guidelines and practices.

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