Reimmunization after bone marrow transplantation. Current recommendations and perspectives

Clarisse M. Machado

Autologous and allogeneic BMT recipients lose immune memory of exposition to infectious agents and vaccines accumulated throughout lifetime and therefore need to be revaccinated. Diphtheria toxoid, tetanus toxoid, pertussis vaccine (children < 7 years old), Haemophilus influenza type B (Hib) conjugate, 23-valent pneumococcal polysaccharide, inactivated influenza vaccine, inactivated polio vaccine and live-attenuated measles-mumps-rubella vaccine are the currently recommended vaccines to be included in a vaccination program after BMT. For most of them, the best time of vaccination, the number of vaccine doses and/or the duration of immunity after vaccination have not been established. Vaccination protocols vary greatly among BMT centers suggesting that the lack of sufficient data has not permitted the establishment of solid recommendations. The use of other vaccines and the perspectives for different vaccination protocols are discussed in this review.

Keywords: Bone marrow transplantation, vaccination, autologous, allogeneic, toxoid, polysaccharide

Introduction

The conditioning regimen used in marrow graft recipients ablates normal and abnormal immunohematopoietic elements and prepares the marrow microenvironment for the donor marrow to develop. The repopulation of the immune system is dependent on appropriate nesting, proliferation, maturation and differentiation of donor cells (1). Ultimately, the recipients lose immune memory of exposure to infectious agents and vaccines accumulated throughout life.

The loss of protective immunity to agents such as tetanus, poliovirus, and measles has been consistently demonstrated in patients submitted to allogeneic and autologous BMT, and consequently a reimmunization program is necessary to ensure immunity (2, 3, 4, 5). Several surveys regarding reimmunization after BMT demonstrated that vaccination protocols vary greatly among BMT centers evidencing that there are insufficient data to establish solid recommendations (6, 7, 8, 9).

This manuscript intends to summarize the current recommendations and highlight the topics that deserve further investigation.

The European Group for Blood and Marrow Transplantation, the Centers for Diseases Control and Prevention, the Infectious Disease Society of America and the American Society of Blood and Marrow Transplantation have recommended that the following vaccines should be included in reimmunization protocols for autologous, syngeneic and allogeneic BMT recipients: Diphtheria toxoid, tetanus toxoid, pertussis vaccine
(children < 7 years old), Haemophilus influenza type B (Hib) conjugate, 23-valent pneumococcal polysaccharide, inactivated influenza vaccine, inactivated polio vaccine and live-attenuated measles-mumps-rubella vaccine.

**Diphtheria toxoid**

Immunity to diphtheria wanes over time. Lum et al. showed that while 100% of the BMT patients with immune donors had antibodies to diphtheria within the first 100 days after transplantation, around 30% of them lost immunity thereafter. Increasing susceptibilities (up to 40%) was noticed in those with chronic graft-versus-host-disease (GVHD) (11).

Other authors, evaluating long-term diphtheria immunity, showed that only 54.5% of the patients still had antibodies to diphtheria with barely protective antitoxin levels one year after BMT (12).

There is evidence that multiple doses are more effective than a single dose in allogeneic recipients without chronic GVHD vaccinated 2 to 6 years after BMT (13).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.

**Tetanus toxoid**

There is contrasting information concerning the persistence of tetanus immunity one year after BMT. Some authors have observed sustained immunity on long-term allogeneic BMT survivors irrespective of toxoid administration pre or post transplantation (11). On the other hand, Ljungman et al. observed that only 50% of the patients who were immune prior to transplantation, sustained tetanus immunity for one year (3).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.

**H. influenza type b conjugate**

Polysaccharides vaccines were not sufficiently immunogenic to the immature immune system of children and the preliminary results of Hib vaccination were disappointing. A new generation of polysaccharide-protein conjugated vaccines were developed and proved to be more immunogenic in children and also in BMT patients. The polysaccharide antigen is conjugated to a protein such as tetanus or diphtheria toxoid or both.

Data from Hib vaccination studies in BMT patients evidenced that at least 2 doses of the conjugated vaccine are necessary to ensure protective antibody levels (22, 23).

Comparing multiple Hib vaccination schedules after BMT, Vance et al. observed that protective levels were achieved after the third or second dose of Hib vaccine in patients starting immunization at 3 or 6 months after BMT, respectively (23).

Parkkali et al. using single dose of diphtheria toxoid showed that while 100% of the BMT patients with immune donors had antibodies to diphtheria within the first 100 days after transplantation, around 30% of them lost immunity thereafter. Increasing susceptibilities (up to 40%) was noticed in those with chronic graft-versus-host-disease (GVHD) (11).

Other authors, evaluating long-term diphtheria immunity, showed that only 54.5% of the patients still had antibodies to diphtheria with barely protective antitoxin levels one year after BMT (12).

There is evidence that multiple doses are more effective than a single dose in allogeneic recipients without chronic GVHD vaccinated 2 to 6 years after BMT (13).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.

**Tetanus toxoid**

There is contrasting information concerning the persistence of tetanus immunity one year after BMT. Some authors have observed sustained immunity on long-term allogeneic BMT survivors irrespective of toxoid administration pre or post transplantation (11). On the other hand, Ljungman et al. observed that only 50% of the patients who were immune prior to transplantation, sustained tetanus immunity for one year (3).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.

**H. influenza type b conjugate**

Polysaccharides vaccines were not sufficiently immunogenic to the immature immune system of children and the preliminary results of Hib vaccination were disappointing. A new generation of polysaccharide-protein conjugated vaccines were developed and proved to be more immunogenic in children and also in BMT patients. The polysaccharide antigen is conjugated to a protein such as tetanus or diphtheria toxoid or both.

Data from Hib vaccination studies in BMT patients evidenced that at least 2 doses of the conjugated vaccine are necessary to ensure protective antibody levels (22, 23).

Comparing multiple Hib vaccination schedules after BMT, Vance et al. observed that protective levels were achieved after the third or second dose of Hib vaccine in patients starting immunization at 3 or 6 months after BMT, respectively (23).

Parkkali et al. using single dose of diphtheria toxoid showed that while 100% of the BMT patients with immune donors had antibodies to diphtheria within the first 100 days after transplantation, around 30% of them lost immunity thereafter. Increasing susceptibilities (up to 40%) was noticed in those with chronic graft-versus-host-disease (GVHD) (11).

Other authors, evaluating long-term diphtheria immunity, showed that only 54.5% of the patients still had antibodies to diphtheria with barely protective antitoxin levels one year after BMT (12).

There is evidence that multiple doses are more effective than a single dose in allogeneic recipients without chronic GVHD vaccinated 2 to 6 years after BMT (13).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.

**Tetanus toxoid**

There is contrasting information concerning the persistence of tetanus immunity one year after BMT. Some authors have observed sustained immunity on long-term allogeneic BMT survivors irrespective of toxoid administration pre or post transplantation (11). On the other hand, Ljungman et al. observed that only 50% of the patients who were immune prior to transplantation, sustained tetanus immunity for one year (3).

Chronic GVHD seems to interfere in response to vaccination 4 months after BMT (9). Although diphtheria vaccination starting one year after transplantation has been mostly recommended, no definitive data is available concerning the best time to start vaccination.
conjugated Hib vaccine, in 45 BMT recipients randomized to start vaccination at 6 or 18 months, observed that both schedules were equally immunogenic (18).

Since the greatest risk for infection by encapsulated bacteria occurs during the first 2 years after BMT, early-start schedules should be preferred in this setting.

Donor and recipient immunization with Hib vaccine before BMT gave more effective results than recipient vaccination after BMT as demonstrated by a higher antibody concentration in patients as early as 3 months post transplantation (20).

Other authors showed that between 4 and 18 months after BMT, the response to Hib vaccination did not correlate with GVHD, use of immunosuppressive drugs or time to vaccination (24).

The results of these studies indicate that at least two doses of Hib conjugated vaccine can be administered safely and effectively as early as 4 months after BMT.

The impact of donor immunization before marrow harvest on the appearance of antibody protective levels soon after BMT must be confirmed in larger, prospective, randomized trials before widely recommended.

**Pneumococcal polysaccharide**

BMT recipients are particularly at risk for developing life-threatening pneumococcal infections due to functional hyposplenism as a result of pre transplant total body irradiation (TBI) and chronic GVHD.

The currently available pneumococcal vaccine contains only pure polysaccharides and requires mature function of the immune system for maximal response. The vaccine is therefore poorly immunogenic in the transplant population. Moreover, this vaccine does not cover 20% of the commonly pathogenic strains and immunized patients remain susceptible to them (9).

Evaluating a 14-valent pneumococcal vaccine in allogeneic BMT patients, Winston et al. observed that pre and post-vaccination levels were significantly lower in BMT recipients as compared to normal control subjects. Multiple regression analysis showed that vaccination within the early post transplant period and corticosteroid therapy of GVHD were the two factors influencing the antibody response (15).

Other authors have also observed decreasing pneumococcal antibody levels over the first year after BMT and poor antibody response to a 23-valent pneumococcal vaccine (16, 17, 18, 19).

Little information is available regarding the impact of GVHD on the response to the pneumococcal vaccine since even non-GVHD patients are poor responders.

Immunization of the donors before marrow harvest did not influence the level of specific antibodies one year or more after transplantation (16, 20).

The data from the majority of the pneumococcal vaccine studies suggest that possibly, the key role affecting response is time to vaccination and consequently, vaccine should be recommended after the second year of transplantation or even later (15, 21). However, impaired serum opsonic activity is expected during the first year after transplantation when life-threatening pneumococcal infections pose greater risk. Thus, the currently available vaccine does not add substantial help in preventing pneumococcal infection during the first year post transplant.

Long-term survivors without chronic GVHD are at lower risk for pneumococcal infection and probably only few of them would benefit from vaccination. Among chronic GVHD patients, the use of corticosteroids affects their response to vaccination, rendering this strategy at least questionable.

Thus, prolonged prophylactic oral penicillin is so far the best option to prevent pneumococcal infection after BMT. The development of a new, immunogenic and safe pneumococcal vaccine is urged.

**Poliovirus vaccine**

Immunity to polio is progressively lost after BMT. Immunocompromised patients and their household contacts should not receive live-attenuated oral poliovirus vaccine (OPV). Thus, inactivated poliovirus vaccine (IPV) is recommended after transplantation.
Ljungman et al. demonstrated that 50% of the patients lost immunity to all 3 poliovirus types one year after BMT. Patients who received 3 IPV doses 12, 13 and 14 months after BMT had significantly higher specific antibodies titers one year later in comparison to patients who received only one dose. GVHD did not interfere on the response to vaccination when the three doses regimen was adopted (4). Other authors have observed similar findings (25).

More recently, Parkkali et al. compared the response to poliovirus vaccination in 45 patients randomized to receive IPV at 6, 8 and 14 months (early group) after BMT or at 18, 20 and 26 months (late group). Both schedules were similarly immunogenic. Acute GVHD accelerated the decrease of poliovirus antibody titers before vaccination but did not interfere with response to IPV. Chronic GVHD did not influence the duration of polio immunity or the response to vaccination (26).

These data suggest that poliovirus immunization also does not need to be postponed for more than 6 months after BMT.

**Influenza vaccine**

Few data are available concerning influenza vaccination after bone marrow transplantation. Engelhard et al. vaccinated 48 patients with two doses of influenza vaccine administered 2 to 82 months after BMT. Vaccination before the sixth month was totally ineffective and the second dose did not add substantial benefit on specific response and its indication is therefore, questionable (32).

Preliminary results of a study evaluating the use of GMCSF (2.5 mg/kg) as an immunomodulating factor to enhance response to influenza vaccination, showed a limited benefit, mostly in those vaccinated before the first year after BMT. Since side effects were not negligible, its use deserves further investigation (33).

**Measles vaccine**

Immunity to measles decreases continuously after BMT (2, 27). Although severe measles is expected to occur in immunocompromised patients, there are only two reports in the literature of measles following transplantation (5, 28).

Probabilities of measles immunity around 47%, 27% and 20% have been reported 3, 5 and 7 years after BMT, respectively (29). Among non-vaccinated BMT recipients, Machado et al. observed that 36.6% were susceptible to measles between the first and second years after BMT and this rate increased to 57.7% after the second year. Type of BMT (allo or auto), acute or chronic GVHD and the use of immunosuppressive drugs did not influence the persistence of immunity in that series (5).

The live attenuated trivalent measles - mumps - rubella vaccine has been administered safely and effectively after the second year of transplantation. Its use has been recommended only in patients not receiving immunosuppressive drugs (2, 7, 9, 10). However, the duration of measles immunity after vaccination and the need of booster doses deserve further investigation in this population.

Among vaccinated patients, Machado et al. observed that 70% had lost measles immunity three years after vaccination suggesting that serological surveillance to check for immunity should be performed in long-term survivors. Moreover, the value and the frequency of booster doses of the vaccine should be better investigated in patients who lost measles immunity (5).

It is important to stress that although most of the recommendations of BMT recipient vaccination are independent of where in the world the patient lives, there are local variations in the scenery of infections that must be taken into account and adjustments in official guidelines are strongly recommended (30).

For example, in 1997, hundreds of BMT recipients were exposed to an outbreak when more than 20,000 cases of measles were diagnosed in the city of São Paulo, Brazil. Eight patients acquired measles and early measles vaccination was the strategy used to avoid the appearance of new measles cases among the patients who had lost specific immunity (5).

To evaluate the safety and effectiveness of this strategy, live attenuated measles-mumps-rubella vaccine was administered one year after BMT to all patients, even those receiving immunosuppressive drugs. No moderate or severe side effect was noted and all susceptible patients responded to
vaccination. The probability of sustained immunity was 60.2% 2 years after early vaccination (31). Thus, this strategy can be safely used in countries that did not achieve measles elimination.

**Varicella vaccine**

No data are available concerning the safety and effectiveness of live-attenuated varicella vaccine before the first year of transplantation, when the risk of VZV reactivation is higher. Sauerberi et al. did not observe any case of chickenpox or herpes zoster for up to two years after vaccination in 15 patients who received one dose of VZV vaccine 12 to 23 months after BMT. These data are difficult to interpret since the occurrence of zoster is expected around the sixth month after transplantation and the risk of a second episode is less than 5% in this population. Thus, few patients would be really “at risk” after the first year of transplantation and the benefit of late vaccination would be minimal (34).

Redman et al. heat-inactivated the live-attenuated vaccine and observed diminished clinical severity of zoster in patients who received 3 doses of the inactivated vaccine 1, 2 and 3 months after BMT. These data suggest that the process of inactivation did not eliminate the immunogenicity of the vaccine, which apparently conferred some protection. This observation requires confirmation in larger studies (35).

**Other vaccines**

Other licensed vaccines such as hepatitis B and hepatitis A have been recommended in individual basis.

Hepatitis B vaccine has been recommended after the first year of BMT in countries where the infection is common and children are routinely immunized against hepatitis B.

In the setting of BMT, hepatitis B vaccine has been evaluated in different circumstances: to immunize susceptible patients after transplantation and also to adoptively transfer HBV immunity through vaccination of the donors before marrow harvest.

Surprisingly, few data is available concerning the effectiveness of hepatitis B vaccine in BMT recipients and the duration of immunity after vaccination.

Nagler et al. observed seroconversion rates around 70% within 40 days of transplantation in autologous BMT recipients receiving single-dose of hepatitis B vaccine immediately before or after transplantation. Transient seroconversion was seen in about 35% of the patients (36).

Ilan et al. demonstrated transfer of hepatitis B immunity in the first 45 days of transplantation from donors vaccinated before marrow harvest (37).

Adopting the classical vaccination schedule proposed for immunocompetent hosts, Machado et al. observed 100% of seroconversion in 50 patients vaccinated after the first year of BMT. However, one year after vaccination nearly 60% of the patients had lost hepatitis B immunity. Sustained immunity was more likely to occur in children and those without chronic GVHD. Interestingly, time to vaccination did not influence the response to vaccination nor the duration of immunity (38).

There are no data on the use of inactivated hepatitis A vaccine in transplant recipients. Considering the efficacy of the vaccine in healthy subjects and the recommendation of vaccination to travelers to endemic areas, it is possible that studies are currently being done. BMT children and those recipients traveling to such areas would benefit from hepatitis A vaccination.

---

**Reimunização após o transplante de medula óssea**

Clarisse M. Machado

**Resumo**

Pacientes submetidos ao transplante de medula óssea, alogênico ou autogênico, perdem sua memória imunológica de exposição a agentes infecciosos e a vacinas adquiridas durante sua vida e necessitam eventualmente serem revacinados. Toxôide difteriano, tetânico e pertussis (crianças < de 7 anos), Haemophilus influenza do tipo B (Hib) conjugada, polissacáride pneumocócica – valência 23, vacina inativada de influenza, vacina de pólio inativada e vacinas vivas atenuadas de sarampo- caxumba- rubéola são as vacinas comumente recomendadas em um programa de vacinação de TMO. No entanto, o momento, número de doses e/ ou o tempo de duração da imunidade após a
vacinação ainda não se encontram estabelecidos. Os protocolos de vacinação entre os vários centros de TMO variam e inexistem dados que propiciem sólidas recomendações. O uso de outras vacinas e perspectivas de diferentes protocolos de vacinação são discutidos nesta revisão.

Palavras-chave: Transplante de medula óssea, vacinação, autogênico, alogênico, toxóide, polissacáride

References

9. Singhal S & Mehta J. Reimmunization after blood or marrow stem cell transplantation.


Recebido: 18/06/2002
Aceito: 22/07/2002