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VERSITA

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Vaccination in children with cancer: a debate

Mini Review

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Abstract: Children with malignancy present an important alteration of the immune system functionality caused by the illness itself and by the therapy they undergo. Therefore, they are at high risk of contracting vaccine-preventable diseases and of developing important complications. Vaccinations represent valid devices against these infections but this condition involves two main problems: are vaccines safe in these patients? Are vaccines effective in these patients?
The aim of this review is to discuss the principles of vaccination management in children with cancer.

Keywords: *Vaccination • Children • Cancer • Immunosuppression*

1. Introduction

Compared to healthy people, patients with cancer have a higher risk of contracting infections and developing serious complications: the high rate of infection among this population results from inappropriate functioning of their immune system. Immunosuppression in children with cancer can be caused by the illness itself, by anti-neoplastic therapy, or both [1-4]. No significant differences in the degree of the immune system impairment have been demonstrated between haematological and solid tumors [4]. The effect of the therapy is evident on all the haematological cellular lines, but low lymphocytes levels appear to persist longer compared with neutrophils, monocytes or platelets, and never seem to return to the pre-treatment values at any time after cessation of therapy [3]. The low level of naive T cells described in these patients can be an important cause of their usually bad response to vaccinations, as described by the attempt to vaccinate patients undergoing chemotherapy against hepatitis B [5,6]. Besides cellular immunity, humoral immunity is affected: abnormally low levels of IgG, IgM and IgA serum concentrations are common in patients who have just completed chemotherapy. Even if good recovery results in nearly all patients within 6 months after completion of therapy, IgG subclass abnormalities or low serum concentration of specific antibodies (vs diphtheria, pertussis and tetanus) can persist for more than one year in a substantial proportion of children [4]. There are relatively few data on the effects of radiotherapy on the immune system, but its impact is certainly less significant than that of chemotherapy.

The type and the intensity of the chemotherapy administered and the age of the patient are the two most important variables in determining the gravity and the duration of immunosuppression after cessation of therapy. Therapies that include agents like cyclophosphamide, purine nucleoside analogs or corticosteroids are extremely immunosuppressive and have a major effect on lymphocyte function, whereas other antineoplastic agents like actinomycin-D and vincristine are not particularly immunosuppressive. Patients who will receive a hematopoietic stem cell transplant (HSCT) usually undergo a pretransplant conditioning regiment with cyclophosphamide and total body irradiation (TBI), which leads to profound and prolonged immunosuppression. Functional hyposplenia or asplenia and thymic atrophy are recognized complications of HSCT, especially when TBI is performed. Younger patients have more persistent immune defects [4]. It is now clear why these young patients are at higher risk of contracting infectious diseases but how this can be prevented remains a matter for debate. Active immunization is commonly accepted as the best way to induce protection against external pathogens in the general population, but its efficacy and safety

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are not clearly demonstrated in immunosuppressed patients. The immunosuppressive effect of chemotherapy persists for a variable period after its cessation [7,8], and there is no unanimous agreement on how much time the immune system needs to reach a recovery sufficiently to have a good response to vaccination. Studies on immunoglobulin levels and immune response to vaccinations show that after 6 months off-therapy there usually is a valid immune recovery [4]; however, that debate continues. Therefore, not only do we need to evaluate the effectiveness of these vaccines, but we also need to assess their safety in these particularly fragile patients: before administrating a vaccine, which is not an essential drug, we have to be absolutely sure that it will not cause the disease it is designed to prevent.

Thus, there are two main topics of debate: on one hand, what is the efficacy of vaccines in patients with a compromised immune system and, on the other hand, the how topic of safety when vaccines are administered to these children.

2. Types of vaccine

A vaccine is a medical preparation that is administered to induce or artificially increase immunity against a specific pathogen and disease. There are several types of vaccines, according to their composition [9]. Live, attenuated vaccine contains a version of the living microbe that has been weakened so that it can't cause the disease; these vaccines are very effective and induce strong cellular and antibodies responses. They often confer lifelong immunity with only one or two doses; however, these vaccines have an important disadvantage namely the remote possibility for the attenuated microbe to revert to a virulent form and cause the disease. Furthermore, these vaccines could also cause the disease in people who have a damaged or weakened immune system and consequently they have to be avoided in these patients. Vaccine against measles, mumps, rubeola, varicella, for example, are live, attenuated vaccines.

On the other hand, inactivated vaccines are created by killing the disease-causing microbe with chemicals, heat or radiation; such vaccines are more stable and safer than live vaccines. Most inactivated vaccines, however, induce a weak immune response and more boosters are usually necessary to reach and maintain protective values. Examples of inactivated vaccines are the vaccine against cholera, against hepatitis A virus, and some types of anti influenza vaccine.

Yet another type is the sub-unit vaccine: instead of the entire microbe, these vaccines include only one to twenty of the pathogen's antigens that best stimulate the immune system; sub-unit vaccines are absolutely safe and reasonably efficacious. The vaccine against hepatitis B virus is a sub-unit vaccine.

If the main cause of the disease is not a bacterium itself but a toxin it produces, toxoid vaccines are the right answer; these vaccines are made of detoxified toxin (toxoid), inactivated in formalin. These vaccines are absolutely safe; one example of this type of vaccine is the anti-tetanus vaccine.

Finally, if a bacterium has an outer coating of polysaccharides that disguise its main antigens so that the immune system is not able to recognise it, what we can use is a conjugated vaccine. Antigens or toxoids from a microbe that the immune system can recognize are linked to the polysaccharides; in this way, the immature immune system becomes capable of reacting against the polysaccharides coating as well, and gives protection against the disease-causing bacterium. The vaccine against Hemophilus influenzae type B is a conjugated vaccine.

3. Safety of vaccinations

Children with cancer who are undergoing chemotherapy or who have suspended the treatment less than 6 months previously are usually immunosuppressed; the intensity of these immune alterations is related to the illness itself but mostly to the chemotherapy or radiotherapy administered; it decreases with time after cessation of therapy [7,8,10].

This condition involves two main problems: are vaccines safe in these patients? Are vaccines effective in these patients? On the first point there is unanimous agreement: since vaccination is used to prevent infections we absolutely can't risk causing the infection we wanted to prevent. That is why all live vaccines are contraindicated in patients with cancer under therapy and within the 6 months after its end (Table 1); thus, MMR vaccine (which is made with live attenuated measles, mumps and rubeola viruses) [11], oral polio vaccine (Sabin), yellow fever vaccine (made with live attenuated yellow fever virus), oral typhoid vaccine (which contains live bacteria that have been weakened) and varicella vaccine (developed from the live attenuated Oka strain of varicella virus) absolutely must be avoided in these patients [12]. Varicella vaccine is not approved for use in children with cancer; focusing on patients with ALL, the 2009 American Academy of Pediatrics guidelines [12] advise that these children should not be routinely immunized where the incidence of Varicella Zoster Virus (VZV) infection is decreasing and that immunization, if necessary, should be undertaken only when at least

Table 1. Types of vaccines and immune response.

Type of vaccine	Examples	Nature of protection	In children with cancer
Live attenuated viruses	Oral Polio, MMR, Varicella	Ig response; cell-mediated immune response	Contraindicated vaccines
Live attenuated bacteria	BCG	Ig response	
Inactivated bacteria/bacterial components	Cholera, Pertussis	Ig response	Allowed vaccines
Subunit vaccines	Tetanus and diphteria toxoid	Ig response	
Killed viruses	IPV, Influenza	Ig response; cell-mediated immune response	
Conjugated vaccines	Pneumococcus, Hib, Meningococcus	Helper T-cell dependent Ig response	
Synthetic vaccines	Hepatitis B (recombinant proteins)	Ig response	

IPV: Inactivated Poliovirus; MMR: Measles,Mumps, Rubella; BCG: Bacillus Calmette-Guérin; Hib: Hemophilus Influenzae Type B

one year has passed after cessation of chemotherapy, under expert guidance and with the availability of antiviral therapy. Some authors suggest that this kind of vaccination should be avoided entirely: first because of the potentially fatal complications of vaccination; second, because of the risk associated with withholding chemotherapy for a variable period before and after the vaccination; and finally, owing to the rarity of death from VZV infection after the first year of treatment for ALL (indeed, most of the deaths from VZV occurred during the early phases of intensive chemotherapy and so could not have been prevented by immunization subsequent to the first year of remission) [13].

On the contrary, inactivated virus vaccines, subunitary, recombining, polysaccharide or toxoid vaccines are safe and can be administrated without problems in patients with cancer (in other words, they do not have a higher risk of vaccine-related events if compared with healthy people). Thus hepatitis A and B vaccine (which are respectively made with inactivated A virus and with a surface protein of B virus, HBsAg) [14], pneumococcal vaccine (which is a conjugated vaccine made with capsular polysaccharides of Streptococcus Pneumoniae) [15], hemophilus influenzae type B vaccine (a conjugated vaccine made with a capsular polysaccharide of HiB) [16], diphteria and tetanus vaccine (which are toxoid vaccines), acellular pertussis vaccine (made with purified antigens of Bordetella Pertussis), inactivated polio vaccine, meningococcal vaccine (made with tetravalent capsular polysaccharide of Neisseria Meningitidis) and killed influenza vaccine can be administered to these patients.

Vaccination against influenza is especially recommended for all immunocompromised patients, including children with cancer, because of their higher risk of adverse outcomes from influenza infection; it have been shown to evoke a good immune response [16,17].

Regarding vaccination against hepatitis A and B viruses, it is really important for those children who live in a high prevalence geographical area, for those who will spend a few months in these regions or for children at risk for other reasons (eg high-risk household, chronic liver diseases). Liver diseases can cause pharmacokinetic alterations that could influence the metabolism of several anti-neoplastic drugs; moreover, the hepatitis B infection in oncological patients has a higher risk of developing into a chronic liver disease [14]. Thus, vaccinating these patients against hepatitis A and B viruses is an important preventive weapon against all these complications.

Children with Hodgkin disease or other hematologic malignancies are known to be at high risk of invasive pneumococcal disease and, therefore, they are in the priority group for pneumococcal vaccination [18].

4. Efficacy of vaccinations

Several studies have demonstrated the certain efficacy of these vaccines if administrated at least 6 months after cessation of chemotherapy without differences attributable to the kind of original tumor (solid vs haematological malignancies) [19,20]. On the other hand, new evidence shows how also vaccines managed within 6 months from the end of therapy [21] or even, in some cases, under therapy, appear to be effective. In Turkey, Meral *et al*. had good outcomes from hepatitis B vaccination to children with cancer at diagnosis: anti-HBs positivity after the first three doses was 77% in children with solid tumors, 88% in those with acute leukemia, and 48% in those with lymphomas [22]. Influenza vaccination is demonstrated to be effective in children undergoing chemotherapy as well, [17] and this vaccination is recommended for all these patients and their relatives.
In conclusion, even if the best timing of vaccine administration in children with malignancy is still matter of de-

bate, what is clear is that only vaccinations administered at least 6 months after cessation of therapy guarantee a good immune response and the achievement of protective antibodies titres.

For this reason, except for influenza vaccination (which is suggested even under chemotherapy), all the other vaccines should be managed at least 6 months after cessation of therapy; nevertheless, in the presence of clinical necessity (such as contacts with people affected by serious vaccine preventable diseases), an early administration of the specific but not live vaccine may be performed, and is eventually associated with passive immunization.

Moreover, still under discussion is what to do with children who have already been vaccinated before diagnosis and before they start chemotherapy. The entire immune system (cellular and humoral immunity) is affected in these patients, so that it is common to find deeply decreased and non-protective immunoglobulin levels. At the end of the treatment, there are different possibilities: the first is to immunize all patients with a booster dose without considering their possible residual immunity. Another approach is to first evaluate the serum level of antibodies against vaccine antigens and then to give a booster dose only to children with no protective levels. The last possibility is to do nothing.

It is a matter for debate how to manage children who have not completed the normal vaccination schedule because of the illness onset [23]: should they restart a new vaccination schedule or should their program be continued? We recommend continuation of the schedule, eventually with the administration of a booster dose at the beginning, if necessary. In conclusion, for all these children (already fully vaccinated or not), our suggestion is to evaluate first the residual immunity to establish whether a new vaccination is required. Then, if necessary, based on the residual immunoglobulin values, decide whether to restart the vaccination schedule, to complete the existing program, or just to administer a booster.

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