

Revaccination in Pediatric Oncology Patients: One Center Experience

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ABSTRACT

Objective: After chemotherapy, cancer survivors suffer from acquired immunological defects and become vulnerable to vaccine-preventable diseases. There are no universally approved revaccination guidelines for non-transplanted oncology patients. This study aimed to share our experience of revaccination in childhood cancer survivors to plan future vaccination schedules.

Materials and Methods: This retrospective study was conducted in a Pediatric Oncology Department of a university-affiliated hospital. Patients who were diagnosed with malignancy other than leukemia constituted the study population. Patients were directed for revaccination 6 months after the cessation of treatment. Revaccination was performed according to patients' vaccination status before chemotherapy and seronegativity.

Results: Of the 64 patients in the study, 44 (68.75%) were boys. The mean age at the time of diagnosis and at start of vaccination was 8.8 ± 5.3 years and 10.6 ± 5.1 years, respectively. Hodgkin's lymphoma was the most common diagnosis. The vaccination schedule of 7 patients was interrupted because of chemotherapy; after completing the missing vaccine doses, the serology of 2 patients was negative for at least 2 antigens. The vaccination schedule of 57 patients was completed before beginning chemotherapy and 52 of them were seronegative for at least 1 antigen. No adverse reactions or life-threatening infections were observed because of vaccinations.

Conclusion: There are different approaches when vaccinating the oncology patients after chemotherapy. Watching out for the four touchstones mentioned in our study will protect the patient and do no harm. More studies are needed to constitute universal and standardized revaccination guidelines for these patients.

Keywords: Vaccination, chemotherapy, pediatric oncology

Introduction

Survival rates have significantly improved in pediatric malignant diseases. Acquired immunological defects occur after chemotherapy in both cell-mediated and humoral immunity, which result in decreased measurable vaccine protection [1]. In these patients, recovery of immune functions has been shown to occur 6–12 months after the completion of chemotherapy [2, 3]. This acquired immunodeficiency poses a risk for life-threatening vaccine-preventable infections for the survivors [4]. Unfortunately, there are no universally approved revaccination guidelines for non-transplanted childhood cancer survivors. Besides, compliance of revaccination in oncology patients has been reported to be poor in clinical settings [5].

Revaccination times after chemotherapy are 3 and 6 months [6, 7]. Furthermore, it is recommended that the patient should be in continuous remission for at least 1 year for varicella vaccinations [8].

In our country, routine vaccination schedules for children include those for diphtheria, pertussis, tetanus, inactivated and oral polio, *Hemophilus influenzae* type B (Hib) (before 5 years of age), conjugated pneumococcus (before 5 years of age), hepatitis B, hepatitis A, varicella, measles, mumps, rubella, and tuberculosis (BCG) antigens. For immunocompromised patients, BCG and oral polio vaccines are not administered, but meningococcus (A, C, Y, and W), Hib (after 5 years), conjugated (after 5 years) and polysaccharide pneumococcus, and seasonal influenza vaccines are recommended in addition to the routine vaccination schedules [9]. However, there are no national vaccination guidelines for revaccination of children after chemotherapy.

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In this study, we share our experience of revaccination in childhood cancer survivors to plan future vaccination schedules.

Materials and Methods

This retrospective study was conducted between March 2016 and May 2019 in the Pediatric Oncology Department of a university-affiliated hospital in Istanbul, Turkey. Patients who were diagnosed with malignancy other than leukemia constituted the study population. Clinical data of each patient were retrospectively reviewed from the patient's medical records. This study was approved by the hospital ethics committee (48670771-514.10) and carried out according to the Declaration of Helsinki protocol.

Patients who died during the therapy ($n=3$), moved to another city for treatment ($n=2$), did not come in for their vaccinations ($n=5$), or had a disease relapse ($n=12$) were excluded from the study. Patients with bone marrow or solid organ transplant were not recruited in the study; only patients with complete data were included. None of the patients received anti-B cell antibody therapy.

In the routine practice of the clinic, 6 months after cessation of treatment, patients were directed to the well-child outpatient clinic for vaccinations. If the vaccination was interrupted because of the treatment, it continued from the point where it had been halted. Only varicella vaccination was given after 1 year of continuous remission. Moreover, meningococcus, Hib, conjugated and polysaccharide pneumococcus (8 weeks after conjugated pneumococcus vaccine), and seasonal influenza (between October and February) vaccines were administered. Furthermore, 1 month after completing the vaccination schedule, serology was tested for measles, mumps, rubella, varicella, hepatitis A, and hepatitis B. If the patient was seronegative for any of these antigens, revaccination was carried out.

For patients who completed their vaccination schedule before chemotherapy, the serologies of measles, mumps, rubella, hepatitis B, hepatitis A, and varicella were checked routinely. If the patients were seronegative for any of these antigens, the vaccine was administered. Moreover, booster

doses for diphtheria, pertussis, tetanus, inactivated polio, Hib, conjugated and polysaccharide pneumococcus (8 weeks after the conjugated pneumococcus vaccine), meningococcus, and seasonal influenza (between October and February) vaccines were administered to all the patients. In addition, 1 month after the last dose of revaccination, the antibody responses were checked. Revaccination was performed for seronegative antigens.

Assessment of patients and revaccination practice is shown in Figure 1.

Anti-hepatitis A IgG and anti-Hbs antibodies were tested with microparticles immunoassay. Rubella IgG, measles IgG, mumps IgG, and varicella zoster IgG were detected using the chemiluminescence method. The results were seropositive or seronegative according to the laboratory test manufacturer's guidelines.

Results

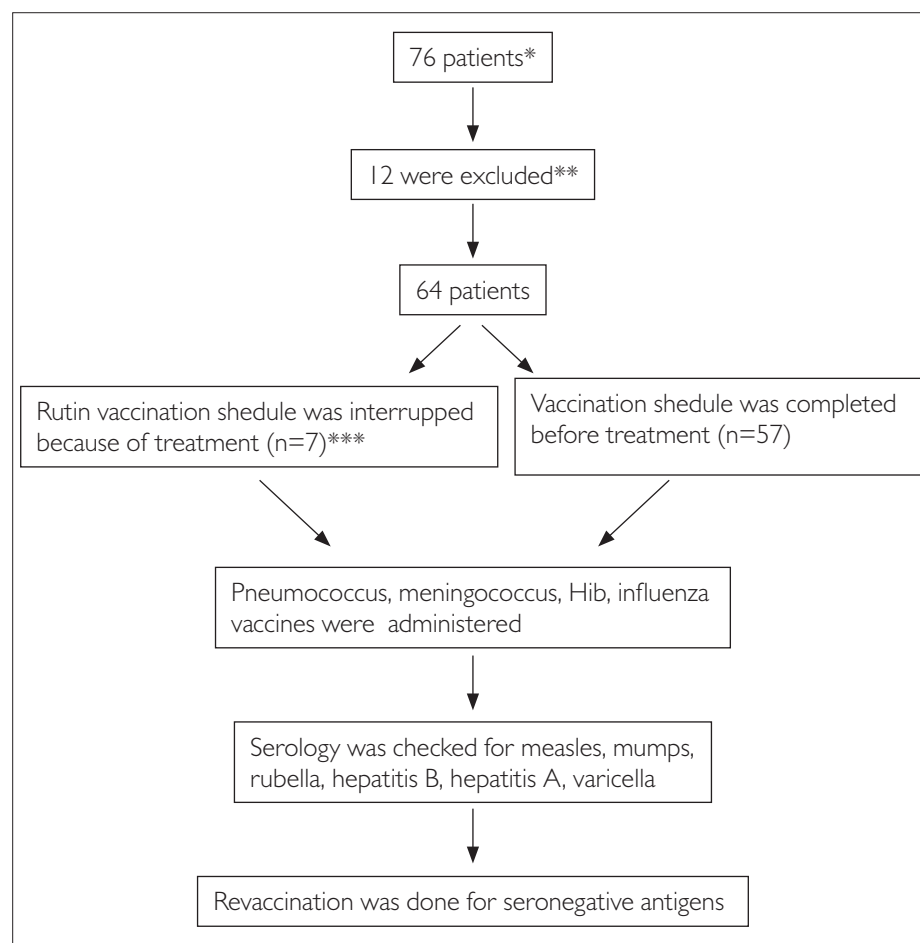
Of the 64 patients, 44 (68.75%) were boys. The mean age at the time of cancer diagnosis and

at the beginning of revaccination was 8.8 ± 5.3 (0.1–17) years and 10.6 ± 5.1 (2–18) years, respectively.

Hodgkin's lymphoma and non-Hodgkin's lymphoma were the most common diagnoses as seen in Table 1.

Serologies were checked after the termination of vaccinations for 7 patients whose vaccinations were resumed. One patient's mumps and varicella serologies were negative, and another's measles, mumps, varicella, and hepatitis A serologies were negative. These patients were revaccinated, and their serologies were positive after the booster doses.

Among 57 patients, only 5 were seropositive for all the 6 antigens. Of 52 (91.2%) patients, 29 (49.2%) were seronegative for measles, 21 (36.8%) for rubella, 29 (49.2%) for mumps, 21 (36.8%) for varicella, 38 (66.6%) for hepatitis A, and 29 (49.2%) for hepatitis B. We administered the vaccinations for seronegative antigens for



*Malignancy other than leukemia

**Missing, moving to another city, not attended revaccination, disease relapsed

***Vaccination was continued from the point it was paused 6 months after the end of treatment

**** Serology was checked, vaccines were administered for seronegative antigens

Figure 1. Assessment of patients and revaccination practice

Main Points

- Checking the serology of vaccine preventable diseases after chemotherapy is useful.
- After chemotherapy, most of the patients were seronegative for the antigens which they had been vaccinated for before.
- More studies are needed to constitute standardized, applicable, and simple revaccination schedules for these patient.

Table 1. Demographic characteristics of patients

	n	%
Sex		
Male	44	68.8
Female	20	31.2
Age at diagnosis Mean±SD	8.8±5.3 years	
Age before vaccination Mean±SD	10.6±5.1 years	
Malignancy types (64)		
Hodgkin's lymphoma	16	25
Non-Hodgkin's lymphoma	15	23.4
Bone tumors	8	12.5
Osteosarcoma (6)		
Ewing sarcoma (1)		
Synovial sarcoma (1)		
Brain tumor	6	9.3
Wilms' tumor	5	7.8
Neuroblastoma	5	7.8
Nasopharyngeal carcinoma	4	6.4
Others	5	7.8
Hepatoblastoma (1)		
Rhabdomyosarcoma (1)		
Testis tumor (1)		
Ovarian germ cell tumor (1)		
Langerhans cell histiocytosis (1)		
Total		

each patient. As we could not test for diphtheria, pertussis, tetanus, polio, Hib, meningococcus, and pneumococcus, booster vaccinations for these antigens were administered to all the patients.

Vaccine serologies were rechecked in 52 patients after the end of the booster doses. Negative serologies were found in 4 patients for mumps, 2 patients for hepatitis A, and 1 patient each for rubella, measles, hepatitis B, and varicella. One more dose of these vaccines was administered, and the serologies were checked again. Furthermore, 5 patients did not consent for serological testing after the last vaccination. No adverse reactions or life-threatening infections were observed during the whole series of vaccinations.

Discussion

For oncology patients, as long as there are no universal revaccination guidelines, every center applies their own schedule according to the country's vaccination practices. Most guidelines are based on the data from healthy children and the experience of the center [10]. In this study, we share our experience considering the 4

touchstones when revaccinating these patients. The first question to be discussed is: "Does this special disease and treatment make any vaccine a contradiction"?

Chemotherapy causes immunosuppression mostly during the induction and consolidation phases. After cessation of treatment, the immune system begins to recover within 3 months or more [11]. There are no contradictions for inactivated or recombinant vaccines for these patients. However, live vaccines can cause vaccine-derived infections for a longer period after the chemotherapy in addition to the possible insufficient immune responses. Oral polio, live attenuated influenza, oral typhoid, yellow fever, and BCG vaccines are contraindicated for cancer patients after treatment [6, 12]. It is better to do Measles-mumps-rubella (MMR) vaccinations 6 months after completion of chemotherapy and varicella 1 year after chemotherapy. In light of the available literature, all the patients were revaccinated after chemotherapy [13-15].

Second, we have to discuss: "When should the patient be vaccinated"?

Although immune recovery has been shown to begin a few months after the discontinuation of chemotherapy, it takes 6-12 months for the immune system to fully recover [2, 3]. The immune reconstitution depends on the nature of the disease, dosing of the treatment, and the age of the patient [16]. After chemotherapy, B-cells and CD8+ T-cells recover after the 3rd month, it takes 6-12 months for CD4+ T-cells to recover [17, 18].

Although early revaccination shortens the patient's unprotected period, in the first 6 months after the therapy, the host may not produce sufficient immunogenicity against the vaccines [2, 13, 19]. Studies generally suggest that it is better to do MMR vaccinations 6 months after and varicella 1 year after the completion of chemotherapy [8, 15].

Our study population was vaccinated with at least a 6-month gap from the cessation of treatment for inactivated/recombinant vaccines and 1 year after for varicella vaccine, consistent with the literature. In the presence of risk for outbreaks of any infection, each patient was discussed separately [20].

The third question was: "Which schedule should be used for revaccination? Should we continue from the point where it was stopped or does the patient need any booster vaccination"?

There are different approaches to this topic. According to Lillian Sung et al. [20], if the vaccina-

tion schedule was not completed, it should be continued from the point at which the child was last vaccinated. According to Esposito et al. [19], the best way is to test the residual immunity and then choose to vaccinate all of the schedule or only a booster. Furthermore, Ruggiero et al. [21] recommended to continue the routine schedule of vaccination 6 months after chemotherapy and then test the residual seroprotectivity. For the patients who did not complete the vaccination schedule, vaccination should be continued from the point where it was stopped [4, 21]. After completing the missed doses, serology was checked, and the patients were revaccinated for the seronegative antigens.

For the patients who completed the vaccination before chemotherapy, 2 options are recommended. The first is administering a booster dose for each antigen and the second is checking the serology and making a vaccination plan for each patient [20, 22, 23]. In our study population, every patient was checked for serology 6 months after the end of chemotherapy. In total, 52 (91.2%) patients were seronegative for at least 1 antigen, and each patient was revaccinated according to the serological findings. Booster doses of the vaccines, which could not be checked for serology, were administered; 1 month after completing the vaccination schedules, the serology was checked again. We cannot argue that this is the best way, but it is more comfortable when revaccinating the vulnerable host.

The last question is, "Does this special disease make any infection riskier? Does the patient need any extra vaccines"?

For cancer patients, both the disease and the chemotherapy cause immune suppression. Furthermore, these patients are at a high risk of invasive pneumococcal and Hemophilus type B infections. It is recommended that the patients should receive both conjugated and polysaccharide pneumococcus, Hib, meningococcal, and inactivated influenza vaccines annually [24-27].

In our country's vaccination schedule, Hib and pneumococcus vaccines are administered only to children under 5 years of age, and meningococcus (A, C, Y, and W) and influenza vaccines are not administered routinely [9]. However, for immunocompromised hosts, these vaccines are offered regardless of age. In our study population, 1 dose of Hib, meningococcus, inactivated influenza, and conjugated and polysaccharide pneumococcus (8 weeks after the conjugated vaccine is administered) vaccines were administered appropriately.

There were some limitations to our study. Because the patients in our study were vulnerable to vaccine-preventable infections, seropositivity was checked for each patient, which may not be cost effective. Every center does not have the opportunity to test the seropositivity for each antigen. It may be simpler or more effective to administer booster doses of vaccines and check the seropositivity later. Each center has the right to implement its own schedule.

In our study, booster doses for diphtheria, pertussis, tetanus, polio, Hib, and pneumococcus antigens were administered, but the serology was not checked. We cannot say that the patients are protected against these antigens as long as we do not test the serology after completing the vaccination.

When revaccinating the pediatric oncology patients, there are different host- and disease-related variables to consider. It is difficult to say that one is better or the other is more effective. The vaccination schedule of the country should be adopted for the specific population. We think that revaccination of patients taking the 4 touchstones mentioned above into consideration will give the best protection and cause the least harm for the children who survived cancer.

In conclusion, there are different revaccination applications for non-transplanted oncology patients. After chemotherapy, most of the patients were seronegative for the antigens, which they had been vaccinated for before; hence, checking the serology after chemotherapy is useful. More studies are needed to constitute standardized, applicable, and simple revaccination schedules for these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Okmeydani Training and Research Hospital (48670771-514.10).

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