Antibody levels against tetanus and diphtheria after polychemotherapy for childhood sarcoma: A report from the Late Effects Surveillance System

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\textbf{Abstract}

\textbf{Background:} It is known that antineoplastic treatment may induce secondary immunodeficiency, but studies after childhood sarcoma are rare. Since 1998, the Late Effects Surveillance System (LESS) of the German Society for Paediatric Oncology and Haematology (GPOH) prospectively registers late effects in soft tissue-, osteo- and Ewing’s sarcoma patients treated within the therapy trials EICESS-92/EURO-E.W.I.N.G.-99, CWS-96/CWS-2002P, COSS-96 in Austria, Germany and Switzerland.

\textbf{Patients and methods:} Antibody levels (AL) against diphtheria and tetanus were used as markers for immunity and classified according to established guidelines for protective AL values. There were 47 eligible relapse-free patients < 21 years of age (31 males; 10 osteosarcoma, 12 Ewing’s and 25 soft tissue sarcoma patients). Median age at diagnosis was 9.6 (interquartile range: 4.4–14.7) years.

\textbf{Results:} A median 7.2 (3.7–12.2) months after end of antineoplastic therapy, in 28% (13/47; 95% CI 16–43%) of patients there were no protective AL (<0.1 IU/ml) against diphtheria and/or tetanus. Diphtheria and tetanus AL were positively correlated (\(r = 0.39\); \(p = 0.007\)). In multivariable analysis, the type of treatment had no effect on AL, similar to tumour type and time of examination after treatment end. Younger patients had significantly lower AL against tetanus (\(p = 0.009\)) and girls had significantly lower AL against diphtheria than boys (\(p = 0.015\)).

\textbf{Conclusion:} Lack of protective AL against tetanus and/or diphtheria is frequent after childhood sarcoma treatment. Prospective surveillance of immunity and, if indicated, re-immunization is warranted in patients treated for childhood cancer.

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1. 

\textbf{Introduction}\textsuperscript{1}

In the past decades, there has been considerable success in paediatric oncology with the development of modern aggressive chemotherapy regimes (MACR). With these therapies about 75% of paediatric cancer patients can be cured in industrial countries [1]. However, with rising numbers of survivors, sequelae of treatment come into the focus of interest. In the United States 1 in 570 individuals between 20 and 34 years of age is a survivor of childhood and adolescent cancer [2]. Follow-up of treatment sequelae thus reaches socioeconomic significance and risk-adapted, standardized aftercare becomes vital for the initiation of secondary and tertiary prevention methods [3].

One important topic in this context is a secondary immunodeficiency induced by cancer treatment [4,5]. It has been established that after MACR treatment, the former patients can exhibit a variety...
of immune system disorders, such as loss of immunity to vaccine-preventable diseases [5–16]. This is an important aspect, since such patients are at risk for infection with vaccine-preventable diseases and could also function as a reservoir for such diseases in the community [5,10]. Most studies to date have examined patients with acute lymphoblastic leukaemia (ALL) and other haematological malignancies [6,7,10,12,14–18]. Data on patients after treatment for solid tumours are rare.

Aim of this study was to determine immunity against vaccine-preventable diseases after MACR treatment for paediatric bone or soft tissue sarcoma, using immunity against diphtheria and tetanus as surrogate markers.

2. Methods

The Late Effects Surveillance System (LESS) is a trinational multicentre study that prospectively registers sequelae of cancer therapy and which has been previously described [19–21]. Follow-up of the patients after antineoplastic treatment is conducted locally by cooperating hospitals and general practitioners according to the national aftercare guidelines, which are formulated by the LESS group and also comprise the study protocol. The results of the examinations are reported to the LESS study centre for collation and analysis. The LESS aftercare network currently comprises 246 hospitals and 60 general practitioners.

Herein we report on relapse-free patients after treatment for Ewing’s-, soft tissue- or osteosarcoma within the trials EICESS-92/EURO-E.W.IN.C.-99, CWS-96/CWS-2002P, COSS-96 in Germany, Austria and Switzerland, who were <21 years of age at diagnosis and did not receive bone marrow or stem cell transplantation during treatment. All studies have been approved by the appropriate ethics committee and written informed consent was obtained from every patient.

Currently, the LESS database encompasses 2879 patients after bone or soft tissue sarcoma, of whom 737 had to be excluded from follow-up registration because of exclusion criteria fulfillment (tumour progression during treatment, the sarcoma being a secondary malignancy, no chemotherapy, unknown previous treatment, treatment not according to a protocol, death under treatment) leaving 2142 eligible patients. On 917 of these patients no follow-up data could be registered. Thus the study population of LESS currently comprises 1225 eligible patients with Ewing’s, osteo- or soft tissue sarcoma. For this analysis, we had to further exclude 28 patients, because they had received an autologous stem cell transplantation. This results in a cohort of 1197 eligible patients.

We have previously reported on other treatment sequelae in the study population [3,22] and the results of this substudy have previously been published in abstract form [23].

Subject of this substudy were antibody titres against vaccine-preventable diseases which were to be observed at 1 and 6 months after cessation of antineoplastic treatment, according to the LESS aftercare guidelines. The recommended measurements were to be carried out at the local hospital conducting follow-up and reported to the LESS study centre.

Only ten hospitals of the LESS-network adhered to the recommendations of the aftercare protocol regarding evaluation of antibody titres versus vaccine-preventable diseases and contributed data to this substudy. Antibody levels against diphtheria and tetanus (DT) were used as surrogates to test secondary immunodeficiency after MACR treatment for bone and soft tissue sarcoma in childhood. According to recommendations of the WHO we used DT antibody titres to evaluate serumimmunity against these diseases, with protective titres suggesting immunity to the respective disease [24,25]. DT-antibody levels < 0.1 IU/ml were not considered protective, in accordance with published guidelines [26].

Recommendations on baseline immunization against diphtheria and tetanus are similar in Austria, Germany and Switzerland, with 4 vaccine doses being recommended until the end of the second year of life. Information on the vaccination status prior to chemotherapy has not been recorded in our database. We used the definition of Zignol et al. [13] and thus examined lack of immunity (in contrast to loss of immunity) in this analysis.

3. Statistical analysis

To estimate the probability of lack of immunity against vaccine-preventable diseases, we calculated proportions with exact 95%-confidence limits. Bivariate analyses of categorical variables were made by Fisher’s exact test, and continuous variables were analyzed using the Mann–Whitney U test or Spearman rank correlation, where appropriate. We used multivariable linear regression models to analyse sex, age at tumour diagnosis, antineoplastic drugs, and time from end of therapy as possible predictors of antibody levels (backwards elimination; exit probability 0.1). Antibody levels were log-transformed to approximate normality. Values given as intervals due to the detection limit (i.e. < 0.1 IU/ml) were analyzed in two ways: (1) using the limit of detection instead, and (2) using normal interval regression, replacing undetectable values with the interval in which the true value could lie (i.e. 0 to limit of detection) [27]. Non-linearity was checked by fractional polynomial regression [28]. Because of fixed drug combinations and small numbers for some drugs, drugs were dichotomized into “yes” or “no” and each drug was analyzed separately. p Values were not adjusted for multiple testing. Analyses were performed using STATA (Version 9.1, StataCorp, College Station, TX, USA). Statistical significance was defined as two-tailed p value of less than, or equal to, 0.05.

4. Results

Forty-seven patients (31 males, 16 females) have been included in this analysis, of whom 10 had been treated for osteosarcoma, 12 for Ewing’s and 25 for soft tissue sarcoma. Table 1 summarizes the received treatment modalities. The median age at diagnosis was 9.6 (interquartile range (IQR): 4.4–14.7) years. Only 7/47 (14.9%) patients had examinations at both specified time-points: in 5 patients immunity status remained unchanged, and 2 patients had lack of immunity against one of the antigens (one against diphtheria, one against tetanus) at the first but restored immunity at the second time-point. In these patients, the first available antibody titre was used for analysis to avoid possible confounding due to unreported booster dose application between measurements.

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Median cumulative dose in mg/m² total body surface area</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin-D</td>
<td>29</td>
<td>9</td>
<td>4.5–9</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>31</td>
<td>240</td>
<td>240–360</td>
</tr>
<tr>
<td>Carboplatinum</td>
<td>10</td>
<td>1500</td>
<td>1500–1500</td>
</tr>
<tr>
<td>Cisplatinum</td>
<td>10</td>
<td>360</td>
<td>240–480</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3</td>
<td>10,500</td>
<td>6600–10,500</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>7</td>
<td>450</td>
<td>450–450</td>
</tr>
<tr>
<td>Etoposide</td>
<td>20</td>
<td>2025</td>
<td>1350–2700</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>34</td>
<td>52,500</td>
<td>24,000–54,000</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10</td>
<td>108,000</td>
<td>48,000–120,000</td>
</tr>
<tr>
<td>Vincristine</td>
<td>29</td>
<td>19.5</td>
<td>19.5–19.5</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>1</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>Trofosfamide</td>
<td>1</td>
<td>3000</td>
<td>–</td>
</tr>
</tbody>
</table>
A median of 7.2 (IQR 3.7–12.2) months after end of treatment the median diphtheria antibody level was 0.25 IU/ml (boys 0.41, girls 0.18 IU/ml), and the median tetanus antibody level was 0.7 IU/ml (boys 0.7, girls 0.89 IU/ml). In 13/47 (27.6%; 95% CI 16–43%) patients there were no protective antibody levels (<0.1 IU/ml) against diphtheria and/or tetanus (Table 2): two patients had no protective titre against tetanus, eight against diphtheria and three against both. A further two patients had unclear diphtheria results (antibody titres <0.15 IU/ml); when classifying these values also as abnormal then 32% (15/47; 95% CI 19–47%) of patients would have had no protective antibody levels. Diphtheria and tetanus antibody levels were positively correlated ($r = 0.39; p = 0.007$). In multivariable analyses, the schedule of antineoplastic treatment, tumour type and time from end of treatment had no significant effect on antibody levels. For diphtheria, girls had significantly lower antibody levels (48%; 95% CI 27–86%) than boys, $p = 0.015$), and there was a tendency of younger patients having lower antibody levels (5%; 95% CI 0–10%) per year younger, $p = 0.058$). Younger patients also had significantly lower antibody levels against tetanus (9%; 95% CI 2–17%) per year younger, $p = 0.009$) whereas there was no statistically significant gender difference ($p = 0.61$). The interval regression analyses confirmed these results.

5. Discussion

In this analysis, we found lack of immunity against tetanus and/or diphtheria in over 25% of examined patients after childhood sarcoma treatment. These results are supported by previous reports including some bone or soft tissue sarcoma patients [8,11,13] and show that not only patients after haematological malignancies develop secondary immunodeficiency, but also after sarcoma treatment. Affected patients possess no immunity against diseases preventable by vaccination and are at risk of contracting these potentially lethal diseases. Whether spontaneous recovery of immunity in former childhood cancer patients occurs is doubtful, and longitudinal data are scarce [7,14].

Antibody levels were lower in younger patients. This association has been previously described for both tetanus and diphtheria antibody levels in ALL patients [12], measles and rubella in ALL patients [10], mumps, tetanus toxoid and varicella in ALL patients [15] and against rubella, mumps, tetanus and measles in a group of patients after various diagnoses [13]. Thus, it would seem that younger children are at increased risk for secondary immunodeficiency after childhood cancer treatment, as it has been previously described also for other treatment toxicities [21,29]. Furthermore, female patients were found to have lower antibody titres against diphtheria. A similar association has been previously described for measles [13]. The reason for these effects has yet to be established [15].

Information on the vaccination status prior to chemotherapy has not been recorded in our data base. However, in Austria, Germany and Switzerland the proportion of children with vaccinations against DT is very high and we can safely assume that nearly all patients had been immunized against these diseases. In the WHO annual report 2005 the percentage of 1-year-olds immunized with 3 doses DT is given as 84% for Austria, 89% for Germany and 95% in Switzerland [30]. Actual immunization rates in older children are even higher as vaccinations are caught-up on and as children receive the 4th dose recommended in these countries until the end of the second year of life. This is supported by a recent study showing that 98% of adolescents in a German population had previously received complete vaccination against DT [31].

The adherence to the study protocol and the follow-up guidelines has not been optimal. This is a problem with multicentre follow-up studies which we have previously described [3,21] and for which solution strategies are being developed. The limiting factor for the low patient numbers that could be included into this analysis was the number of hospitals that performed and subsequently reported AL measurements against DT. In a recent Australian audit, poor compliance with guidelines for post-chemotherapy revaccination of childhood cancer survivors has already been described [32]. We aim to improve this drastically in the future via improved dissemination of good clinical practice guidelines. This result clearly underlines that there is still a tangible need for information regarding sequelae of childhood cancer treatment, even in institutions that already care for such patients.

In the present context, this is further aggravated by the fact that the management of patients after childhood cancer treatment with regards to immunity against vaccine-preventable diseases is still controversial, and that there are various recommendations by different groups [9,26,33–39]. Our results in sarcoma patients and previously published studies clearly show that patients after MACR treatment are at risk for lack of immunity against vaccine-preventable diseases and emphasize the need for antibody titre evaluation after treatment. However, the presence of seroimmunity as shown by protective antibody titres cannot be equalled to total protection from contracting the disease, even in immunocompetent individuals, as there have been previous reports of tetanus and diphtheria in patients with protective antibody levels; the presence of these diseases remains a clinical diagnosis, irrelevant of antibody titre [40–43].

Furthermore, application of booster doses in patients that have already completed their base immunization schedule without first determining relevant AL might be more economic [34,44]. In Germany, a booster dose of combined DT vaccine costs approximately 66% of what AL determination for DT would cost (taking into account only laboratory costs within the hospital performing follow-up). However, as not all patients would receive a booster dose after AL determination, it is not possible to provide a recommendation based on the economic aspect of this issue; this should be evaluated in separate studies with an appropriate design.

Based upon these results, our recommendation is in concordance to previously published guidelines [26,45]. If indicated, patients should receive a booster dose and success of vaccination controlled and documented via antibody titre examination. Patients after treatment for cancer should receive inactivated vaccines at the earliest 3 months after cessation of all antineoplastic treatment and live vaccines at the earliest after 1 year in remission after cessation of all antineoplastic treatment, if permitted by their lymphocyte count ($>1500/\mu l$) [26].

References


