Prospective evaluation of hepatitis B, C and HIV infections as possible sequelae of antineoplastic treatment in paediatric sarcoma patients: A report from the Late Effects Surveillance System

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Abstract. Cancer therapy and supportive measures entail the risk of infection with hepatitis B (HBV), hepatitis C (HCV) or human immunodeficiency virus (HIV). The objective of this analysis was to establish the incidence of infections with these viruses during antineoplastic treatment in our paediatric sarcoma patients, who are being followed-up within the Late Effects Surveillance System (LESS), which prospectively registers sequelae of therapy for Ewing’s-, soft tissue- and osteosarcoma in patients treated in Germany, Austria and Switzerland within the trials EICESS-92/EURO-E.W.I.N.G.-99, CWS-96/CWS-2002P and COSS-96. We studied 264 eligible relapse-free paediatric patients [median age at diagnosis 14.3 (IQR 11.1-16.4) years], treated from January 7, 1998 until April 24, 2004. According to the LESS protocol, serological examinations for HBV, HCV and HIV were scheduled 4 weeks and 6 months after cessation of antineoplastic treatment. The median follow-up was 20.6 (IQR 12.4-26) months. None of the patients was reported to have acquired HBV, HCV or HIV during antineoplastic treatment. Blood donor screening and prophylactic measures employed in Germany, Austria and Switzerland to prevent infections of cancer patients with HBV, HCV and HIV seem to be very effective, having fully prevented new infections in this large cohort of paediatric sarcoma patients.

Introduction

Patients receiving cancer therapy are at risk of infection with a multitude of agents. These include infections with hepatitis B (HBV), hepatitis C (HCV) or human immunodeficiency virus (HIV). In cancer patients, infection with these viruses is mainly iatrogenic in non-endemic areas, for example through transfusion of contaminated blood products (1), immune globulins (2), or contaminated equipment (3). Fulminant hepatitis (1,4), chronic hepatitis (1,5) as well as chronic carrier status (4-7), cirrhosis (6,8,9), hepatitis failure (6,8) and hepatocellular carcinoma (6) have been described in HBV- and/or HCV- infected cancer patients. However, evaluations of these virus infections are rare for large homogeneous cohorts of paediatric cancer patients, especially in children that have risk factors for infection other than transfusions, such as major surgery (10).

The aim of this analysis was to determine the cumulative incidence of infections with HBV, HCV and HIV during antineoplastic therapy within a homogeneous population of relapse-free, prospectively examined, paediatric sarcoma patients.
Materials and methods

The Late Effects Surveillance System (LESS) is a multinational multicentre study that prospectively registers sequelae of cancer therapy. Herein we report on patients with Ewing’s-, soft tissue- and osteosarcoma treated in Germany, Austria and Switzerland (11-14) within the trials EICESS-92/ EURO-E.W.I.N.G.-99, CWS-96/CWS-2002P, COSS-96. All studies have been approved by an ethics committee and a written informed consent was available for every patient. We have previously reported on treatment toxicities in our study population (15).

According to the LESS protocol, serological examinations for HBV, HCV and HIV are scheduled 4 weeks and 6 months after cessation of antineoplastic treatment and are carried out at the hospital or general practitioner conducting follow-up. No specific examinations are prescribed. Only positivity or negativity for the respective viruses is reported to the LESS centre. Basic hepatic examinations include clinical examination (scheduled at least every 3 months in the first and second year, with lower frequency in subsequent years) and at least yearly examinations of transaminase and bilirubin concentrations in the patient serum (11,12).

Since January 1, 1998, 1780 patients have been included in the LESS-study. Follow-up within the LESS-study ceases when relapse or a second malignancy occur. For this analysis, we excluded patients >21 years of age, patients with stem cell transplantation, patients who had no reported follow-up at both aforementioned examination points and those who had been identified as being infected prior to the initiation of antineoplastic treatment. Thus, 486 patients were eligible.

Statistical analysis. Bivariate analyses of categorical variables were made by Fisher's exact test, and continuous variables were analysed using the Mann-Whitney U test. All analyses were performed using SAS (version 8.2, SAS Institute Inc., Cary, NC). Statistical significance was defined as two-tailed p-value of ≤0.05.

Results

There were 486 eligible relapse-free paediatric patients who had presented for follow-up at both examinations at 4 weeks and 6 months after the end of antineoplastic therapy. However, in 222 (46%) of these patients no results for virus tests were reported or the appropriate tests were not done, which left 264 patients with at least one reported result (Table I).

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Table I. Characteristics of the patient groups with and without reported results for HBV, HCV and HIV examinations. a

<table>
<thead>
<tr>
<th></th>
<th>Patients with at least one reported result</th>
<th>Patients with no reported results</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=264</td>
<td>N=222</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>148 (56%)</td>
<td>110 (49.5%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Female</td>
<td>116 (44%)</td>
<td>112 (50.5%)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing’s</td>
<td>81 (30.7%)</td>
<td>45 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>83 (31.4%)</td>
<td>64 (28.8%)</td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>100 (37.9%)</td>
<td>113 (50.9%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Median age at</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis in years</td>
<td>(IQR 11.1-16.4)</td>
<td>(IQR 11.9-16.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Median follow-up</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>in months</td>
<td>(IQR 12.4-26)</td>
<td>(IQR 24.2-51.1)</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>199</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>No report</td>
<td>52</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>13</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>E1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>244</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>No report</td>
<td>13</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>7</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

aE0, examination at 4 weeks after end of therapy. E1, examination at 6 months after end of therapy. All patients in both groups presented for both these follow-up examinations. IQR, interquartile range.
Table II. Characteristics of patients with viral infections diagnosed before antineoplastic therapy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Malignancy</th>
<th>Age at cancer diagnosis in years</th>
<th>Follow-up in months</th>
<th>Virus infection(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>Osteosarcoma</td>
<td>19</td>
<td>55</td>
<td>Hepatitis B, Hepatitis C</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>Osteosarcoma</td>
<td>17</td>
<td>64</td>
<td>Hepatitis B, Hepatitis C</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>Ewing’s sarcoma</td>
<td>10</td>
<td>56</td>
<td>Hepatitis C, Hepatitis G</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Ewing’s sarcoma</td>
<td>10</td>
<td>28</td>
<td>Hepatitis B, Hepatitis C</td>
</tr>
</tbody>
</table>

and in length of follow-up (longer in patients without reported virus examination results). None of the 264 patients were reported to have acquired HBV, HCV or HIV during antineoplastic treatment.

Hepatic status was reported in 261 of the 264 patients with at least one reported virus serology status. There were no reports of sustained high liver function tests or other indications for hepatitis. There were, however, four patients who had been excluded from analysis for positive examination results already diagnosed before cancer therapy. Their details are given in Table II.

Discussion

No examined patient treated within our sarcoma trials from January 7, 1998 until April 24, 2004 was reported as having been infected with HBV, HCV or HIV under antineoplastic treatment. Our results indicate that blood product screening (16-18) and prophylactic measures (1) employed in Austria, Germany and Switzerland seem to be sufficient to protect paediatric cancer patients from infection with HBV, HCV or HIV.

It has been recently stated that transfusion of blood products has become a very safe therapeutic modality (2,3,18,19) and it seems that invasive procedures, which have been previously described as risk factors for infection with aforementioned viruses (7,10), are also safe when managed properly (10).

The safety of blood products is supported by reports showing very low risks of infection with HBV, HCV and HIV through blood transfusion in industrial countries in the last years, with estimated residual risks per million donations for HBV, HCV and HIV being 1.66-13.88, 0.1-6.69 and 0.14-1.95 respectively (17,20-24).

Studies on paediatric cancer patients transfused before routine HCV testing of blood products became available, report highly variable cumulative incidences of ≤2% for HBV and/or HCV, depending on country and endemic environment (6,7,9,25,26). In endemic environments, even after the introduction of routine HCV testing of blood products, there have been reported rates of 12.9-19.2% seropositivity for HBV and/or HCV in paediatric cancer patients (4,10).

An early German study in adults undergoing surgery for various diseases, including cancers, reported newly acquired hepatitis in 6.7% of transfused patients and in 0.65% of non-transfused patients (27,28). In Germany, anti-hepatitis B serum antigen (HBsAg) testing was introduced widely in the early 70s and became compulsory in 1977, while anti-hepatitis B core antigen (HBc) testing commenced around 1975, though remaining elective until today, just like HBV nucleic acid testing (NAT) has. Testing for anti-HCV was widely introduced in 1990 and HCV-NAT is compulsory since April 1, 1999 (October 1, 1999 for fresh frozen plasma). Regarding HIV, anti-HIV testing is compulsory since October 1, 1985 and HIV-NAT since April 30, 2004.

Thus, our patients were treated in an era of standardised serological donor blood screening, in contrast to those reported upon in aforementioned early study in Germany, since at their hospital there was only anti-HBsAg screening available at that time, having been newly introduced in 1970.

As the LESS-study has been conceived as part of a vertical cost effective network, sophisticated examinations such as HBV-NAT are not mandatory so as to enable all participating follow-up institutions, from university hospitals to general practitioners, to conduct the follow-up using widely available means. We included only those patients into this analysis, who had presented for both follow-up examinations at which serological virus tests were scheduled. Of the eligible patients, 46% had no reported result or no virus test at either of the two scheduled examinations. For further investigation, we analysed the years in which patients of the groups with and without reported results were diagnosed and found that there is a significant difference between patients in earlier years of the study and patients in recent years, with more recently diagnosed patients having more frequently reported results for virus examinations. This is probably due to a change of methodology that was instituted in the LESS-study. Up until 2001, only positive results had to be reported. After 2001, a new form was introduced for reporting any result. This could also explain the difference in length of follow-up. Those patients without a reported virus test result are likely to have been diagnosed in the early phase, thus having longer follow-up.

There was also a statistically significant difference between the two groups regarding tumour type. We cannot really explain this difference, as the late effects follow-up recommendations for all these sarcomas are very similar. We have discussed the methodological problems of data return and data completeness in the LESS-study previously in detail (14).

To complement our results, we also reviewed reported hepatic status in this study population. There were no reports...
of sustained high transaminase or bilirubin serum levels or other indicators for hepatitis. Nevertheless, there remains a possibility that infections were not detected or were underestimated, causing underestimation of cumulative incidences.

A limitation of our study is that no detailed data on transfused blood products were available. However, patients that are treated in centres farther away from their residence often receive supportive therapy, such as transfusions, in local hospitals and it has also been previously reported that clinical patient records often do not fully correspond with transfusion service records (29,30). Since most of our patients received major surgery and all of them had very intensive polychemotherapy, it is safe to assume that most of them will have had at least one transfusion (7).

These results on cumulative incidence of HBV, HCV and HIV infections acquired under sarcoma therapy including polychemotherapy suggest that in industrialised countries attention must shift to combating other types of transfusion-transmitted infections and other consequences of transfusion, such as immunologic reactions and, of course, preventable human error (16,19,31-36).

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References