Secondary tumours following etoposide containing therapy for germ cell cancer


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Summary

Background: Reports have implied etoposide as the cause of secondary leukaemia in patients treated for germ cell cancer.

Patients and methods: Between 1979 and 1992, 679 male patients with germ cell cancer received etoposide containing chemotherapy.

Results: Six of 679 patients developed acute myeloid leukaemia (relative risk 150; CI: 55–326). None of these patients had a primary mediastinal germ cell tumour and only 1 patient received previous radiotherapy. The median interval between the onset of cytotoxic treatment and the development of leukaemia was 27 months. The FAB M4 morphology was seen in 4 of 6 cases.

Conclusion: The benefit of etoposide containing protocols outweigh the risk of leukaemia in patients with intermediate or high risk disease, however in patients with good risk disease non-etoposide containing protocols should be explored.

Key words: etoposide, germ cell tumours, secondary leukaemia

Introduction

Metastatic testicular cancer has become one of the most curable solid neoplasms: In the 1970's only 10 percent survived, whereas the overall survival in the 1990's is 90 percent. This dramatic improvement resulted primarily from the introduction of effective multidrug cisplatin-based chemotherapeutic regimens [1].

From 1981 through 1984, the Southeastern Cancer Study Group conducted a randomized prospective study comparing cisplatin, vinblastine and bleomycin (PVB) with cisplatin, etoposide and bleomycin (BEP) as initial induction chemotherapy for metastatic germ cell cancer. The 2 year survival rate was approximately 80% in both arms, with a slight, but not statistically significant survival advantage for BEP. However, in the group of patients with advanced disseminated disease, there was a clear survival advantage for the etoposide containing regimen (p = 0.02). There was also a statistical and clinically significant reduction in neuromuscular toxicity associated with BEP. As a result of this phase III trial, the BEP regimen is now widely used in the management of germ cell cancer [2].

At Charing Cross Hospital the POMB/ACE regimen has been used since 1978 and incorporates 7 of the most active agents in germ cell cancer. This regimen can cure more than 60% of patients with advanced bulky disease teratoma [3]. There have been recent reports of leukaemia following combination chemotherapy including etoposide which raises a question over whether the undoubtedly reduced acute toxicity and enhanced efficacy compared with PVB have been achieved at the expense of this late complication [4–6].

We report here on the incidence of secondary cancer in 679 patients with advanced germ cell cancer treated with etoposide containing protocols. This is the first report of secondary cancers associated with the POMB/ACE regimen, where a higher incidence might have been expected due to the inclusion of an alkylating agent (cyclophosphamide) and another intercalating agent (Actinomycin D).

Materials and methods

From January 1979 until December 1992, 679 previously untreated male patients with germ cell cancer were treated with etoposide containing therapy at Charing Cross Hospital and The Royal London Hospital (RLH). Of these 343 (50.5%) were treated with etoposide in the POMB/ACE regimen at Charing Cross Hospital [3] whilst 336 (49.5%) were treated with etoposide in the POMB/ACE regimen at Charing Cross Hospital [3] whilst 336 (49.5%) were treated at the RLH with previously reported schedules [7, 8] combining etoposide with platinum and bleomycin (Table 1). Information collected from the databases at these two hospitals included primary site of the tumour, histology, stage, date of starting chemotherapy, age at starting therapy, treatment protocol, number of cycles of therapy, total cumulative dose of etoposide, date of completion of chemotherapy, further radiotherapy (RT), further salvage chemotherapy, response, date of last follow-up and the development of any further malignancy. Patients who did not achieve a complete remission or who died of germ cell cancer were not excluded from the analysis. Duration of follow-up was calculated from the initiation of chemotherapy until the date of last follow-up. Germ cell tumours were classified according to the British
Table 1. Chemotherapy protocols.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Etoposide</th>
<th>Cisplatin</th>
<th>Vinblastine</th>
<th>Bleomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEVIP</td>
<td>120 mg/m²</td>
<td>20 mg</td>
<td>4.5</td>
<td>30 IU</td>
</tr>
<tr>
<td>No. of days</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>BEP</td>
<td>120 mg/m²</td>
<td>20 mg</td>
<td>30 IU</td>
<td></td>
</tr>
<tr>
<td>EBCa</td>
<td>120 mg/m²</td>
<td>15 IU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMP/ACE</td>
<td>300</td>
<td>120</td>
<td>30 IU</td>
<td></td>
</tr>
<tr>
<td>POMP</td>
<td>0.5 mg</td>
<td></td>
<td>500</td>
<td></td>
</tr>
</tbody>
</table>

AUC: Area under the curve; IU: International Units; Cyclophos: Cyclophosphamide.

Histological Classification and staging was based on the Royal Marsden classification system [9]. Morphologic classification of AML was based on the French-American-British (FAB) criteria.

In order to calculate the ratio of observed to expected number of cases of AML, sex and 5 year age group specific rates of new registrations of AML were taken from the figures compiled by the Office of Population Censuses and Surveys (OPCS) for England and Wales [10]. The rates for all leukaemias except lymphoid were taken, that is ICD9 205-208, which for all ages have a rate of 6.0 per 100,000. The OPCS rates are not broken down into the subcodes which differentiate between acute and chronic leukaemia. However we can estimate the proportion of acute cases that make up the total, by reference to published U.S. figures from where we estimate the proportion of acute cases to be 56% [11]. The personyears programme was used to perform the computation which gave an expected total number of cases of 0.07 [12].

Results

Table 2 summarizes the characteristics of 679 patients treated from January 1979 until December 1992 with etoposide containing regimens. Of these 529 (78%) are alive, 109 (16%) are dead and 31 (4.5%) were lost to follow-up. The median age was 27.5 years. The follow-up data are summarized in Table 3. The median follow-up for patients still alive was 68 months, 541 (80%) were followed-up for more than 2 years and 331 (49%) for more than 5 years.

Six patients (0.88%) in this population developed acute myeloid leukaemia (tAML) and a further 4 patients (0.6%) a solid tumour (excluding cancer of the contra-lateral testis).

The characteristics of the six patients who developed secondary leukaemia are summarized in Table 4. None of these patients had a primary mediastinal germ cell tumour and only 1 patient had previous radiotherapy. The median interval between the onset of treatment
Table 4. Characteristics of patients developing tAML.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Primary site and histology</th>
<th>Chemotherapy</th>
<th>Cumulative etoposide dose, mg/m²</th>
<th>Other treatment</th>
<th>Interval between onset/completion of chemotherapy and leukaemia (months)</th>
<th>FAB type and cytogenetics</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>34</td>
<td>Testis MTI</td>
<td>BVP × 1 BEP × 2</td>
<td>720</td>
<td>RPLND</td>
<td>66/63 months</td>
<td>M1 49XY +8 +2 t(13; 15) t(17; 21)</td>
<td>24</td>
</tr>
<tr>
<td>2.</td>
<td>36</td>
<td>Testis MTU + Seminoma</td>
<td>PVB × 2 BEP × 2</td>
<td>750</td>
<td>RT</td>
<td>27/24 months</td>
<td>M4 Normal</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td>32</td>
<td>Testis MTU</td>
<td>EBCa × 4</td>
<td>1440</td>
<td>RPLND</td>
<td>10/7 months</td>
<td>M2 11q23</td>
<td>22+</td>
</tr>
<tr>
<td>4.</td>
<td>17</td>
<td>Testis MTU + Seminoma</td>
<td>POMB/ACE</td>
<td>5000</td>
<td>RPLND</td>
<td>96/24 months</td>
<td>M4 Normal</td>
<td>3</td>
</tr>
<tr>
<td>5.</td>
<td>35</td>
<td>Testis MTT + Seminoma</td>
<td>POMB/ACE</td>
<td>900</td>
<td>NIL</td>
<td>30/26 months</td>
<td>M4 t(8; 21)(q22; q22)</td>
<td>30</td>
</tr>
<tr>
<td>6.</td>
<td>30</td>
<td>Testis MTI</td>
<td>POMB/ACE</td>
<td>3000</td>
<td>NIL</td>
<td>16/6 months</td>
<td>M4 Not done</td>
<td>10</td>
</tr>
</tbody>
</table>

α INF: Alpha Interferon; RT: radiotherapy; MTI: malignant teratoma intermediate; MTT: malignant teratoma trophoblastic; MTU: malignant teratoma undifferentiated.

and the development of leukaemia was 27 months. The FAB M4 morphology was seen in 4 of 6 cases, with the expected cytogenetic abnormalities (11q23 and t(8; 21)) seen in 2/5 cases tested. Five of 6 patients attained a clinical remission from their leukaemia with chemotherapy, but 4 of these have since relapsed and died. Patient number 4 and 6 had refractory testicular cancer, were treated over a prolonged period of time with various combinations of cisplatin and etoposide and patient number 4 died of AML whilst still having large residual para-aortic nodes containing mature teratoma.

Making the adjustment for acute cases only, we have expected a value of 0.04 cases compared to an observed number of 6 and hence a relative risk of 150 (95% confidence interval = 55–326). Comparing this to a Poisson variate we have a p-value of <0.001.

Table 5 shows the number of patients who developed tAML relative to the cumulative dose of etoposide received. Two of 25 (8%) who received more than 2000 mg/m² developed tAML, whereas 4 of 636 (0.6%) who received less than 2000 mg/m² developed tAML (p = 0.02).

Of anecdotal interest there were four patients who developed solid cancers: 1 melanoma after EBCa, 1 squamous carcinoma of the lung after POMB/ACE, 1 squamous carcinoma of the larynx after BEP and 1 squamous carcinoma of the oesophagus after POMB/ACE.

Table 5. Cumulative etoposide dose.

<table>
<thead>
<tr>
<th>mg/m²</th>
<th>No. of patients</th>
<th>tAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–500</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>500–1000</td>
<td>186</td>
<td>3</td>
</tr>
<tr>
<td>1000–1500</td>
<td>404</td>
<td>1</td>
</tr>
<tr>
<td>1500–2000</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>679</td>
<td>6 (0.88%)</td>
</tr>
<tr>
<td>&lt;2000</td>
<td>636</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>25</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>p = 0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

In a cohort of 679 male patients treated with etoposide containing protocols for germ cell cancer we found a relative risk of 150 of developing tAML.

Two types of tAML are now recognized: One is induced by treatment with an alkylating agent, has a long latent period, is usually preceded by myelodysplasia, and is occasionally associated with unbalanced rearrangements of chromosome 5 and/or 7 [13, 14]. The second type has a short latent period, no preleukaemic phase, and has cytogenetic abnormalities associated with primary AML: Including 11q23 rearrangements or t(8; 21). This second type is associated with agents that target DNA topoisomerase II [15].

Table 6 summarises the reports of tAML associated
Patients with testicular venous or lymphatic invasion by low risk sub-groups for the development of recurrence. The primary tumour can divide patients into high risk and surveillance policies and shown that approximately 30% of men with stage I NSGCT develop metastatic therapy. Two prospective MRC studies have evaluated tous testis cancer include surveillance, retroperitoneal it seems unlikely [18].

Mens for ALL not exposed to cisplatin and bleomycin (bleomycin, vincristine, cisplatin alternating with etoposide). Patients with germ cell cancer who receive >2000 mg/m² of etoposide are at risk of tAML following PVB, in large groups of patients treated with etoposide containing regimens for germ cell cancer [4, 5, 6, 16]. Of the 212 patients reported by Pedersen-Bjergaard, 84 received >2000 mg/m² and all 5 secondary haematological malignancies occurred in this group. Recently, the Memorial Sloan Kettering Cancer Centre (MSKCC) and Indiana University published the incidence of secondary leukaemia in their patients treated with BEP. The incidence was lower than previously reported by Pedersen-Bjergaard. However, Indiana University only included patients treated with a cumulative dose of <2000 mg/m² and the MSKCC only included patients who achieved a durable complete remission. Hannover University reported 1 case of acute lymphoblastic leukaemia in 221 patients treated with 2000 mg/m² or less of etoposide.

In this series of 679 patients with germ cell cancer we confirm the risk associated with etoposide containing regimens. Although this risk in patients with germ cell cancer is dose related, tAML does occur at low cumulative doses of treatment (0.6% of patients treated with less than 2000 mg/m²). Patients with germ cell cancer who receive >2000 mg/m² of etoposide are at particular risk of developing TAML.

Although there have been anecdotal case reports of tAML following PVB, in large groups of patients treated with PVB no increase risk was observed [16, 17]. Whether cisplatin, bleomycin or other drugs contribute to the increase incidence of tAML in etoposide containing regimens cannot be determined from the current data, but given the incidence of TAML with similar characteristics in children treated with etoposide regimens for ALL not exposed to cisplatin and bleomycin it seems unlikely [18].

Current strategies to manage stage I non-seminomatous testis cancer include surveillance, retroperitoneal lymphnode dissection (RPLND) or adjuvant chemotherapy. Two prospective MRC studies have evaluated surveillance policies and shown that approximately 30% of men with stage I NSGCT develop metastatic disease [19]. However, histopathological analysis of the primary tumour can divide patients into high risk and low risk sub-groups for the development of recurrence. Patients with testicular venous or lymphatic invasion by tumour have a 62% relapse free survival (RFS) compared to a 85% RFS for patients without these ‘high risk’ features [20]. The majority of patients with low risk stage I disease will receive adjuvant chemotherapy unnecessarily, therefore these patients are best managed with a surveillance program.

Nearly all men with poor risk stage I disease will be cured with salvage chemotherapy should they relapse, therefore unnecessarily exposing these patients to potential leukaemogenic protocols is unacceptable. The relapse rate after 2 cycles of adjuvant BEP for high risk stage I disease is 5% [21]. The Royal London Hospital treated 25 patients with high risk stage I teratoma with 1 cycle of adjuvant BEP of whom 2 patients have relapsed (unpublished data), suggesting that 1 cycle BEP is inadequate adjuvant therapy. Because etoposide is the drug principally responsible for alopecia, myelo-suppression and leukaemogenesis, the MRC is currently conducting a trial of 2 cycles of BOP (bleomycin, vincristine and cisplatin) to treat patients with high risk stage I teratoma.

Patients with stage II non-seminomatous testis cancer (with nodes <3 cm) are currently managed with RPLND in the USA, of which the long-term side-effects are well established; or 3–4 courses of BEP chemotherapy. The survival in this group of patients after RPLND and salvage chemotherapy approaches 98% [22]. Although RPLND has not been routinely used in stage II patients in the UK, the standard therapy for these patients has been chemotherapy, with disease free survival of 97% reported [23]. Even in this group of patients with an excellent prognosis, unnecessary exposure to agents with potential long term toxicity is not advisable. If we are going to pursue upfront chemotherapy for these patients we should explore other protocols. The POMB regimen (without ACE) is not associated with secondary neoplasms [24] and might be of value in this setting, although only a large phase III study comparing POMB with BEP will resolve this problem. Another option is 3 cycles of PVB, where we can expect a lower incidence of neurotoxicity than reported after 4 cycles.

In patients in the intermediate risk metastatic non-seminomatous germ cell cancer groups, such as those defined by the MRC prognostic factor analysis [25], the benefit of etoposide containing regimens outweigh the risk of TAML or secondary solid cancers as these patients should never receive more than 2000 mg/m² etoposide, and the leukaemia incidence was only 4 of 636 (0.6%) in this group.

In patients with poor prognostic germ cell cancer who are less likely to be cured with 4 cycles of BEP (<2000 mg/m² etoposide), the risk of tAML might be reduced by treatment with POMB/ACE or BOP/VIP (bleomycin, vincristine, cisplatin alternating with etoposide, ifosfamide and cisplatin). However, compromising in etoposide dose intensity by adding less effective drugs and the addition of another leukaemogenic agent may be counterproductive. The MRC and

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No. AML (%)</th>
<th>Cumulative etoposide dose (mg/m²) for those developing TAML</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>5 (2.4)</td>
<td>All &gt;2000</td>
<td>Pedersen-Bjergaard*</td>
</tr>
<tr>
<td>340</td>
<td>2 (0.6)</td>
<td>1300 and 2000</td>
<td>Bajorin²</td>
</tr>
<tr>
<td>538</td>
<td>2 (0.37)</td>
<td>Both &lt;2000</td>
<td>Nichols⁴</td>
</tr>
<tr>
<td>221</td>
<td>1* (0.45)</td>
<td>2000</td>
<td>Bokemeyer¹⁶</td>
</tr>
<tr>
<td>679</td>
<td>6 (0.88)</td>
<td>720, 750, 900, 1440, 3000 and 5000</td>
<td>Current report</td>
</tr>
<tr>
<td>1990</td>
<td>16 (0.8)</td>
<td>Total</td>
<td>Total</td>
</tr>
</tbody>
</table>

* One patient developed acute lymphoblastic leukaemia
EORTC are currently comparing 6 cycles of BEP (cumulative etoposide dose 3000 mg/m$^2$) to 6 cycles of BOP/VIP (cumulative etoposide dose 900 mg/m$^2$).

Preliminary results from 2 phase III studies failed to show any short term advantage (acute toxicity or CR rate) of VIP over PEB (26, 27). The EORTC randomized patients with intermediate risk disease, whilst Indiana University treated patients with advanced disease. Although myelotoxicity was greater in the VIP arm in both studies, the long term toxicities (including secondary neoplasms) associated with VIP is not known.

At this stage the incidence of second solid tumours is too low to be statistically significant. However we now know that the latency period for the development of secondary solid tumours after chemotherapy for Hodgkins disease or radiotherapy for seminoma is longer than leukaemia. Therefore further follow-up for this cohort of patients will be necessary to fully ascertain their risk [28, 29].

In Hodgkins lymphoma those patients treated with MOPP, have a 10-, to 60-fold increased incidence of leukaemia [30]. However, the incidence is substantially reduced with the use of a regimen of equal efficacy and lower leukaemogenic potential, the ABVD protocol [31–33]. Currently various groups are incorporating etoposide into first line protocols for this disease. Although new investigational protocols with potential therapeutic superiority over current protocols should not be abandoned prematurely, the investigation of etoposide containing regimens in patients with good risk disease should proceed with caution. The BEP protocol was used for more than 10 years, before the risk of tAML was appreciated.

In conclusion this paper effectively reminds us of the need for all patients cured of cancer to have life long follow-up to establish the long term risks attached to the various treatment modalities.

References


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