Long-term follow-up after risk-adapted treatment in clinical stage 1 (CS1) nonseminomatous germ-cell testicular cancer (NSGCT) implementing adjuvant CVB chemotherapy. A SWENOTECA study


1Department of Oncology, St Olavs University Hospital, Trondheim, Norway; 2Department of Oncology–Pathology, Karolinska Institute and University Hospital, Stockholm, Sweden; 3Department of Oncology, Haukeland University Hospital and Section of Oncology, Institute of Medicine, University of Bergen, Bergen, Norway; 4Department of Oncology, Sahlgrenska University Hospital, Gothenburg; 5Department of Oncology, Lund University Hospital, Lund, Sweden; 6Institute of Clinical Medicine, University of Tromsø and 7Department of Oncology, Ålesund Hospital, Ålesund, Norway

Received 1 September 2009; revised 10 December 2009; accepted 7 January 2010

Background: To offer minimized risk-adapted adjuvant treatment on a community and nationwide basis for patients with clinical stage 1 (CS1) nonseminomatous germ-cell testicular cancer (NSGCT). The aim was to reduce the risk of relapse and thereby reducing the need of later salvage chemotherapy while maintaining a high cure rate.

Patients and methods: From July 1995 to January 1998, a total of 232 Swedish and Norwegian patients were treated for CS1 NSGCT. All were eligible for inclusion into one of two community-based multicenter Swedish and Norwegian Testicular Cancer Project (SWENOTECA) III studies. One study was a prospective randomized study for patients without vascular invasion in the testicular tumor (VASC₂), evaluating the effect of one adjuvant course of cisplatin, vinblastine and bleomycin (CVB) compared with surveillance. The second study was a prospective study evaluating the effect of two adjuvant courses of CVB for VASC+ patients.

Results: Due to slow accrual and emerging data on toxicity of CVB, the studies were prematurely closed for inclusion in 1998. Of the 232 CS1 patients treated during the study period, only 97 were included in the studies. As all remaining patients were managed according to the SWENOTECA III protocol, although not randomized, the data were pooled. At a median follow-up of 10.1 years, there have been 24 relapses. While one course of CVB to VASC₂ patients had limited effect on the relapse rate, two courses of adjuvant CVB reduced the relapse rate among VASC+ patients by >90%. Toxicity was high in patients administered adjuvant CVB as 24% of patients experienced grade 3 or 4 obstipation/ileus and 23% grade 3 or 4 infection.

Conclusions: There was no statistical difference in relapse rate between one course of adjuvant CVB and surveillance for VASC₂ NSGCT patients. Two courses of adjuvant CVB for VASC+ NSGCT patients reduced the relapse rate with >90% in comparison to the surveillance group. Toxicity was unacceptably high for all patients receiving CVB. Adjuvant CVB chemotherapy has no place in the treatment of CS1 NSGCT.

Key words: adjuvant chemotherapy, clinical stage 1, long-term follow-up, risk-adapted treatment, testicular cancer

introduction

Germ-cell tumors of the testis are the predominant type of malignancy in men 15–35 years of age, although it only accounts for 1%–2% of all male malignancies. Over the last decades, there has been a steady increase in the annual incidence in most Western countries, and Scandinavia is a high endemic area [1]. The age-standardized incidence rate in Norway was 12.1 in 2007, which is the highest reported in the world [2].

About half the patients are diagnosed with seminomatous and nonseminomatous histology, respectively. Of the patients with nonseminomatous germ-cell testicular cancer (NSGCT), ~50% have clinically detectable metastases at the time of orchiectomy. From large surveillance series, we know that ~25%–30% of patients diagnosed with clinical stage 1 (CS1) disease are destined to relapse due to subclinical disease not detected during staging procedures [3]. The management of CS1 NSGCT is controversial. Retroperitoneal lymph node dissection (RPLND), surveillance and adjuvant chemotherapy (ACT) all yield survival rates of 98%–99% [3]. The adverse effects of the different approaches are however different. Dependent upon...
risk factors, >50% of patients with CSI NSGCT are cured by orchiectomy alone [4]. The current aim in the management of CSI NSGCT is to reduce treatment-related acute and long-term toxicity, while maintaining or improving survival.

prognostic factors in CS1 nonseminoma
There have been several studies to investigate the prognostic factors for occult metastatic disease in CSI NSGCT. The single most important prognostic factor regarding risk of relapse is invasion of tumor cells into blood or lymphatic vessels in the testicular tumor (VASC) [4–7]. Using only VASC status, patients can be discriminated into groups with low risk or high risk of relapse. Patients with VASC+ tumors have a 3-year relapse rate of ~50% [5, 6, 8, 9]. Data from surveillance series show that patients without vascular invasion have a relapse risk of 10%–20% [5, 6, 8, 9].

Swedish and Norwegian Testicular Cancer Project
The Swedish and Norwegian Testicular Cancer Project (SWENOTECA) started in 1981 with the SWENOTECA management program for staging, treatment and follow-up of NSGCT. On the basis of data from SWENOTECA I [4, 7], a new protocol for NSGCT, SWENOTECA II, was implemented in 1991. According to the SWENOTECA II, patients with CSI NSGCT were managed with a risk-adapted approach. Risk adaptation was on the basis of a combination of VASC status (VASC+/−) and elevated preorchietomy levels of α-fetoprotein (AFP+−). Patients with a low relapse risk (VASC−, AFP+) underwent surveillance, patients with an intermediate relapse risk (VASC+−, AFP+−) underwent diagnostic RPLND and patients with a high relapse risk (VASC+, AFP−) were offered three courses of adjuvant BEP (bleomycin, etoposide and cisplatin) chemotherapy. The analysis of the SWENOTECA II prospective study encompassing 250 patients formed the basis for the study (SWENOTECA III) presented herein [10].

patients and methods
From July 1995 to January 1998, a total of 232 Swedish and Norwegian CSI NSGCT patients were treated according to the SWENOTECA III protocol. The protocol included two community-based multicenter SWENOTECA studies. The studies planned to evaluate a risk-adapted approach to treatment of CSI NSGCT.

The first study was a prospective randomized study for patients without vascular invasion (VASC−), evaluating the effect of one adjuvant cycle of cisplatin, vinblastine and bleomycin (CVB) compared with surveillance.

The second study was a prospective study evaluating the effect of two adjuvant cycles of CVB for VASC+ patients.

The patients underwent clinical staging at the time of orchiectomy. Definitive stage was not confirmed until a new restaging procedure had taken place 6 to 8 weeks after orchiectomy. The staging procedure included clinical examination, computed tomography (CT) of the thorax, abdomen and pelvis and serum tumor markers [β-human chorionic gonadotropin (β-hCG), AFP and lactate dehydrogenase] measured before, directly after orchiectomy and weekly until restaging 6–8 weeks later. The patients were staged using the Royal Marsden Hospital staging system [11]. All patients were followed prospectively according to the same follow-up schedule, this also included nonrandomized patients and patients treated outside of protocol. On the basis of poor accrual in the VASC− study and increasing data on CVB toxicity, the studies were closed prematurely for inclusion of new patients in 1998. Due to the low number of patients in the randomized study and as the nonrandomized patients were staged, treated and followed according to the SWENOTECA III protocol, results are published pooled according to treatment given and VASC status.

chemistry
The choice of CVB as ACT was on the basis of reports of cisplatin-based ACT in CS2 patients after RPLND and high-risk CSI [7, 12]. CVB was chosen over BEP because of initial concern regarding the risk of BEP-induced myelogenous leukemia [13]. There was also concern of resistance to later salvage BEP chemotherapy if one course of BEP was given in the adjuvant setting. CVB courses were administered with the following doses, repeated after 21 days for patients receiving two courses: cisplatin 20 mg/m2 daily, day 1–5; vinblastine 0.15 mg/kg, day 1 and 2 and bleomycin 30 mg, day 1, 5 and 15. The maximum dose of vinblastine given was 11 mg per day and 22 mg per cycle. In patients with reduced renal function, the cisplatin dose was adjusted according to renal clearance.

follow-up
The patients were followed according to the SWENOTECA III protocol. The first 2 years, serum tumor markers were measured every second month; year 3, every third month and year 4 and 5, every sixth month. CT/magnetic resonance imaging (MRI) of the abdomen and pelvis was scheduled every second month during the first 8 months, then every fourth month during year 2 and every sixth month during year 3–5. Abdominal ultrasound every second year was allowed in patients suitable for this examination. Clinical examination and pulmonary X-ray were scheduled every second month, years 1–2; every third month, year 3 and every sixth month, years 4–5. Yearly checkups were scheduled during years 6–10 with clinical examination, pulmonary X-ray and tumor markers.

toxicity
Short-term toxicity, including hematological, renal, gastrointestinal, pulmonary, neurological and infectious complications, was graded according to World Health Organization (WHO).

population
All Swedish centers report to the SWENOTECA database. Furthermore, the SWENOTECA database is cross-checked yearly with the Swedish National Cancer Registry, ensuring that all patients diagnosed with CSI NSGCT during the current time frame were included. Only five hospitals treat and stage testicular cancer in Norway, four of which reported to the SWENOTECA database. Completeness of the Norwegian data is on the basis of thorough searches in the hospital databases and cross-checked with the SWENOTECA database. The survival status of all patients was checked against the national population registries in Sweden and Norway as of 1 May 2009. The SWENOTECA management program was approved by the Swedish and Norwegian Medical Ethical Committees.

statistics
Relapse-free survival and overall survival were calculated with the Kaplan–Meier method from the date of orchiectomy [14]. The log-rank test was used to compare groups. Only two-sided P values are reported. A P value of <0.05 was considered statistically significant. All statistical calculations are carried out using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL).

results
A total of 232 patients were included from four Norwegian and 18 Swedish centers (Table 1). Median age at orchiectomy was 29.5 years [interquartile range (IQR) 24.7–35.7] with a range of...
Table 1. Cumulative relapse rates, time to relapse and duration of follow-up

<table>
<thead>
<tr>
<th>Risk group</th>
<th>ACT</th>
<th>Number of patients</th>
<th>Relapse</th>
<th>Kaplan–Meier relapse rate (%)</th>
<th>Time to relapse (years)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>232</td>
<td>24</td>
<td>10.3</td>
<td>7.9</td>
<td>0.8</td>
<td>0.2–10.7</td>
<td>10.1</td>
</tr>
<tr>
<td>VASC+</td>
<td>None</td>
<td>5</td>
<td>3</td>
<td>60</td>
<td>60</td>
<td>0.6</td>
<td>0.3–1.0</td>
</tr>
<tr>
<td>VASC+</td>
<td>CVB × 1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>VASC+</td>
<td>CVB × 2</td>
<td>55</td>
<td>1</td>
<td>1.8</td>
<td>0.9</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>VASC+</td>
<td>CVB + BEP</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>VASC–</td>
<td>None</td>
<td>124</td>
<td>16</td>
<td>12.9</td>
<td>13.0</td>
<td>0.7</td>
<td>0.2–5.1</td>
</tr>
<tr>
<td>VASC–</td>
<td>CVB × 1</td>
<td>40</td>
<td>4</td>
<td>10</td>
<td>14.7</td>
<td>1.8</td>
<td>0.3–10.7</td>
</tr>
<tr>
<td>VASC?</td>
<td>CVB × 1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

ACT, adjuvant chemotherapy; VASC+, with vascular invasion; CVB, cisplatin, vinblastine and bleomycin; BEP, bleomycin, etoposide and cisplatin; VASC–, without vascular invasion; VASC?, uncertainty regarding vascular invasion.

16.0–82.1 years. The median follow-up time was 122 months (IQR 91–138) and a minimum follow-up of 13 months. Only three patients had <46 months follow-up, due to emigration and patients lack of compliance. Follow-up regarding deaths are complete, with a median follow-up of 149 months. Three patients have died. Two patients allocated to surveillance have died, one died of heart failure at 87 years of age and the other of pneumonia at 70 years. One patient receiving two courses of adjuvant CVB chemotherapy died 9 years after ACT of infectious hepatitis at an age of 76 years. This gives a disease-specific survival of 100% and an overall survival of 98.4%.

VASC– patients

CVB × 1. Forty patients received one course of CVB adjuvant, 17 after randomization and 23 not randomized. Median follow-up time was 123 months with IQR 99–139 and a minimum follow-up time of 27 months. The four relapses after adjuvant CVB chemotherapy occurred 1, 10, 27 and 126 months after completion of ACT. The relapse occurring immediately after ACT was localized in the lungs and treated with four courses of BEP. The remaining three relapses occurred in the abdomen. They all had normal AFP and β-hCG at relapse and were treated with RPLND. In the relapse after 10 months, histology showed mature teratoma, and no supplemental therapy was given. In the last two cases, histology showed seminoma, and the patients received postsurgical BEP chemotherapy and are today free of disease. In the case of the very late relapse, this occurred in a para-aortal lymph node, which was slightly enlarged already at initial staging. In hindsight, this patient had a misclassified CS IIA disease.

surveillance

One hundred and twenty-four patients were allocated to surveillance, 20 of them after randomization. Median follow-up time was 123 months with IQR 89–139 and a minimum follow-up time of 13 months. There were 16 relapses. Fifteen occurred within the first 15 months of orchiectomy, the last patient relapsed after 51 months. Ten relapses were located to the abdomen, two were pulmonary only, three were tumor marker positive only and one had disseminated disease including the liver. Three abdominal relapses were initially treated with RPLND. One had mature teratoma and received no further treatment. One had embryonal carcinoma and received three courses of BEP following RPLND. The last patient had a biopsy-verified seminomatous relapse in a right-sided iliacal lymph node. Following biopsy, this patient was treated with four courses of etoposide and cisplatin. Initially, this patient had synchronous bilateral testicular cancer, with left-sided CS1 VASC– nonseminoma and right-sided CS1 VASC+ seminoma. The remaining 13 relapses following surveillance all received initial salvage chemotherapy. Supplemental surgery, in the form of RPLND or lumpectomy in the lungs was carried out in 9 of these 13 relapses. In four of these, the histology showed mature teratoma, and in five no pathology/necrosis were found. All relapsing patients are alive and without evidence of disease.

VASC+ patients

CVB × 2. Sixty patients with VASC+ CS1 NSGCT were allocated to receive two courses of CVB ACT. Fifty-five patients completed two courses of adjuvant CVB. Due to toxicity after the first course of CVB, four patients switched to BEP for the second course. One patient discontinued ACT due to toxicity after one course of CVB. Median follow-up was 116 months with IQR 87–128 and a minimum follow-up of 16 months. One patient died of infectious hepatitis almost 9 years after completing the CVB chemotherapy, without any sign of relapse. There was only one relapse in patients planned to receive two courses of CVB. It occurred in the abdomen 2 months after completion of the second course of CVB and was treated with RPLND (mature teratoma). The patient did not receive additional treatment and is today free of disease.

treatment outside protocol

Five VASC+ patients got no adjuvant treatment, and two received only one course of adjuvant CVB. Median follow-up time is 110 months with IQR 100–128 and minimum follow-up time is 79 months. Three of the five VASC+ patients followed by surveillance relapsed, and all relapses occurred within 12 months after orchiectomy. Two relapses occurred in the abdomen and one in the lungs. All were treated with initial salvage BEP chemotherapy and are alive without evidence of disease. None of the two patients given one course of CVB relapsed.
short-term toxicity
Dependent upon category, toxicity was reported for 90%–95% of patients. There was minimal difference in toxicity between patients receiving one or two courses of CVB. WHO grade 3 or 4 constipation affected 23 (27%) of the patients receiving CVB. Ten of these patients (12%) suffered paralytic ileus and were hospitalized. Twenty-one patients (25%) were hospitalized due to neutropenic infections. Grade 3 and 4 leukopenia affected 53 patients (60%). Three (4%) patients experienced grade 3 neuropathy. Pulmonary, renal and thrombocytic toxicity were low, with no reported grade 3 or 4 toxicity.

discussion
The use of ACT in CS1 NSGCT has since its introduction been controversial. Adjuvant treatment is not needed to prevent relapse for the majority of patients. Our population-based material supports that >85% of VASC– are cured by orchiectomy alone. Although were few VASC+ patients were treated by orchiectomy alone, the data, together with other supplemental published data from the SWENOTECA group, support that ~50% of VASC+ patients are cured by orchiectomy alone [9]. However, any treatment required in the case of relapse may cause substantial morbidity and, though rare, mortality.

The rationale for giving ACT is to minimize the number of patients being exposed to salvage chemotherapy. As long-term chemotherapy side-effects increases by the number of chemotherapy cycles given, the aim is to minimize side-effects without reducing outcome. Both paternity and metabolic syndrome are negatively affected with an increasing number of chemotherapy courses [15–17]. In long-term survivors of testicular cancer, secondary malignancies, mainly leukemia and bladder cancer, are associated with previous chemotherapy [18, 19]. The dose of etoposide with two courses of BEP is 1.0 g/m², and no increase of secondary leukemia in patients receiving <1.2 g/m² of etoposide has been shown [20]. The risk of cardiovascular disease is higher in long-term survivors of testicular cancer and is associated with high cumulative dose of cisplatin-based chemotherapy [21, 22]. The psychological burden from having a relapse is poorly studied but is also a factor the physician should take into account when discussing adjuvant treatment with the patient.

We now report, to the best of our knowledge, the first study on the use of one course of adjuvant CVB chemotherapy in CS1 NSGCT.

The adjuvant effect of one course of CVB chemotherapy in VASC– patients was disappointing, with 4 of 40 patients (10%) relapsing. In comparison, only 16 of 124 VASC– patients (13%) not given adjuvant treatment relapsed (Figure 1). The effect of two CVB courses in VASC+ patients was as expected with a cumulative relapse rate <2%, which corroborate other studies on two adjuvant courses of CVB, BEP and BOP (bleomycin, vincristine and cisplatin) [9, 23, 24].

CVB chemotherapy resulted in unacceptable toxicity as 30% (31 of 103) of the patients receiving either one or two courses of adjuvant CVB required hospitalization due to paralytic ileus or neutropenic infection. The high degree of toxicity was unexpected on the basis of SWENOTECA’s earlier experiences.

We speculate whether the introduction of new antiemetics in the form of 5-hydroxytryptamine-3 antagonists combined with the high doses of vinblastine aggravated the abdominal side-effects, when compared with the high doses of metoclopramide used as standard antiemetics in the earlier years of CVB chemotherapy. A prospective study from the Norwegian Radium Hospital has previously reported a high incidence of paralytic ileus (51%) with 31% of patients requiring short-term hospitalization after CVB chemotherapy [25]. The current study and the study from the Norwegian Radium Hospital emphasize the importance of prospective collection of toxicity data to evaluate side-effects.

The high toxicity of the CVB regimen affected accrual to the randomized VASC+ study and was the reason for the premature closure of the two studies. As a consequence of this,
most VASC− patients were followed with surveillance. VASC− patients receiving adjuvant CVB outside of the randomized study were mainly patients with a strong preference regarding ACT. The fact that data have been pooled, following the low accrual in the two studies, creates a potential bias. The SWENOTECA III protocol was revised, and the results of adjuvant BEP in CS1 NSGCT were recently published [9]. Regarding long-term follow-up, a British and a Swiss series of patients, receiving one course of ACT, have been published [26, 27]. With a median follow-up time of >10 and >8 years, there were no reports of late relapses. Both these series used BEP ACT. There are several reports on long-term follow-up after two courses of cisplatin-based ACT [23, 24, 28–30]. With median follow-up of between 70 and 113 months, there were no reports of late relapses. In our study, where the ACT did not include etoposide, we had one late relapse at 126 months with histological verified vitall germ-cell tumor. However, this patient most likely had CS2A disease at staging, but he was staged CS1 and managed as such. Due to radiological misinterpretation, this recurrence should have been diagnosed and treated accordingly several years earlier. This late relapse along with the high relapse rate among VASC− patients treated with CVB are of interest. Although the numbers are small, they emphasize the possible danger of implementing adjuvant treatment without adequate potency, both with regard to the occurrence of relapses and the risk of late relapses. It should act as a cautionary note to the use of ACT regimens with known lower potency, e.g. single-course carboplatin for CS1 seminoma patients. In such patients, sustained and scrutinized follow-up is mandatory.

There are no solid data on the late effects of one or two courses of ACT, making long-term toxicity of short ACT a theme of controversy. We believe that the risk of long-term toxicity of chemotherapy is minimum additive, if not synergistic with increasing courses of chemotherapy. We hope that term data on toxicity from the large cohort of patients treated by the SWENOTECA with one course of BEP will provide some information regarding this controversial question [9].

The intensity of abdominal imaging with CT is also a question of concern. Frequent low-dose radiation exposure will give a small but important risk of radiation-induced secondary cancer. In the current SWENOTECA protocols, MRI is preferred as abdominal imaging modality, and the intensity of imaging is less frequent.

In conclusion, survival for CS1 NSGCT patients treated and followed with a rigorous management program is excellent. With a relapse rate of 13% (Kaplan–Meier), the data verify the numbers are low, the data concerning VASC patients again confirm that about half of these patients will relapse without treatment. Due to toxicity and inadequate efficacy, adjuvant CVB has no place in the adjuvant setting of CS1 NSGCT.

acknowledgements

We thank all patients, investigators and institutions involved in this study. We also thank Monika Andersson at the Tumorregisteret in Lund, Sweden, for the collection of data.

references


