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Long-term outcome of patients with clinical stage I high-risk nonseminomatous germ-cell tumors 15 years after one adjuvant cycle of bleomycin, etoposide, and cisplatin chemotherapy

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Background: To report the long-term results of adjuvant treatment with one cycle of modified bleomycin, etoposide, and cisplatin (BEP) in patients with clinical stage I (CS I) nonseminomatous germ-cell tumors (NSGCT) at high risk of relapse.

Patients and methods: In a single-arm, phase II clinical trial, 40 patients with CS I NSGCT with vascular invasion and/or >50% embryonal cell carcinoma in the orchiectomy specimen received one cycle of adjuvant BEP (20 mg/m² bleomycin as a continuous infusion over 24 h, 120 mg/m² etoposide and 40 mg/m² cisplatin each on days 1–3). Primary end point was the relapse rate.

Results: Median follow-up was 186 months. One patient (2.5%) had a pulmonary relapse 13 months after one BEP and died after three additional cycles of BEP chemotherapy. Three patients (7.5%) presented with a contralateral metachronous testicular tumor, and three (7.5%) developed a secondary malignancy. Three patients (7.5%) reported intermittent tinnitus and one had grade 2 peripheral polyneuropathy (2.5%).

Conclusions: Adjuvant chemotherapy with one cycle of modified-BEP is a feasible and safe treatment of patients with CS I NSGCT at high risk of relapse. In these patients, it appears to be an alternative to two cycles of BEP and to have a lower relapse rate than retroperitoneal lymph node dissection. If confirmed by other centers, 1 cycle of adjuvant BEP chemotherapy should become a first-line treatment option for this group of patients.

Key words: testicular cancer, chemotherapy, adjuvant therapy, high-risk

introduction

Patients with clinical stage I (CS I) nonseminomatous germ-cell tumors (NSGCT) with vascular invasion (VI) have a 46%–50% risk of relapse [1]. Positive retroperitoneal lymph nodes are present in 20%–58% of cases, particularly when >50% embryonal cell carcinoma (EC) components are found in the orchiectomy specimen. Lymph node metastases are also seen in most patients with pure EC plus VI [2]; hence, VI and EC >50% are risk factors for relapse [3].

Treatment of CS I NSGCT remains controversial. Various guidelines recommend a risk-adapted approach: active surveillance with deferred treatment upon relapse, or adjuvant chemotherapy, or retroperitoneal lymph node dissection (RPLND), followed by chemotherapy if necessary [4, 5]. All three modalities achieve equivalent cure rates of 98%–99% [6].

Patients under active surveillance have recurrence rates between 25% and 50% depending on their risk factors [1]. To achieve a cure rate of 95%–100% with salvage chemotherapy [6], three to four cycles of bleomycin, etoposide, and cisplatin (BEP) are required.

RPLND is the only procedure to detect and remove lymph node micrometastases. Its main drawbacks are an up to 29% risk

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of relapse despite the procedure, perioperative morbidity, and loss of antegrade ejaculation [2, 6, 7].

Two cycles of BEP chemotherapy are recommended for patients with high-risk CS I NSGCT with very low recurrence rates [7–13]. The main concerns, however, are toxicity with cardiovascular morbidity, neuropathy, renal toxicity, impaired fertility, and secondary malignancies [14].

We and other groups have evaluated a single cycle of BEP as an alternative to two courses [11, 12, 15–18]. We therefore present long-term follow-up data of our patient cohort (median follow-up of 15 years).

patients and methods

Between 1995 and 1999, 44 patients with newly diagnosed, high-risk CS I NSGCT with VI and/or EC >50% were enrolled in a prospective, single-arm, phase II clinical trial. The study was approved by the local ethics committee and adhered to the Declaration of Helsinki.

All patients were clinically staged with abdomino-pelvic computed tomography (CT), chest X-ray ($n=12$) or CT ($n=28$), and serum tumor markers (α -fetoprotein, β -human chorionic gonadotrophin, and lactate dehydrogenase) before and after orchiectomy. Normal serum markers after orchiectomy and no evidence of metastatic disease were required for study inclusion. For histological examination, multiple tissue sections were taken <1 cm apart, paraffin-embedded, and stained with hematoxylin and eosin. Tumors were classified according to the WHO and TNM classifications [19, 20]. Immunohistochemical staining was used to confirm the presence of VI. Slides were reviewed by an experienced uropathologist (EKD).

Patients underwent chemotherapy within 4 weeks after orchiectomy. All patients received 1 modified-BEP cycle with a daily dose of 20 mg/m² of bleomycin (given as a continuous i.v. infusion over 24 h to decrease the risk of pulmonary side-effects), 120 mg/m² of etoposide and 40 mg/m² of cisplatin administered i.v. on days 1–3.

Patients were followed every 3 months (years 1 and 2), and every 6 months (years 3–5) with history, physical examination, and serum tumor markers. Chest X-ray, CT, or ultrasound of the abdomen, blood counts, and serum chemistry were carried out biannually until year 5. Thereafter patients were evaluated annually with physical examination and tumor markers until year 10. Imaging of the remaining testis, chest, and retroperitoneum were only carried out upon suspicion of relapse. After year 10, laboratory and imaging examinations were carried out only upon suspicion of relapse and surviving patients were contacted by phone. Late adverse events were graded according to National Cancer Institute criteria [21].

Primary end point was the rate of relapse after adjuvant chemotherapy, with or without elevation of tumor markers. Secondary end points were rates of metachronous testicular tumors, secondary neoplasia, and late post-chemotherapy toxicity. Intervals to relapse, death, or secondary malignancies were calculated from the date of orchiectomy.

results

A total of 44 patients entered the study. Four were excluded from the analysis: three had <50% of EC upon histopathological reevaluation, and one patient insisted on receiving two BEP cycles. Median age of the remaining 40 patients at the time of surgery was 33 (range: 18–44) years. Twenty-three patients had pT1 (57.5%), 16 pT2 (40%), and 1 (2.5%) pT3 disease. Twenty-three patients had >50% of EC (57.5%), 16 VI, and >50% of EC (40%) and 1 with <50% of EC with pronounced VI in the surgical specimen (2.5%).

Median follow-up was 186 (range: 10–224) months, with 34 patients (82.5%) followed for >120 months. One patient (2.5%) had a pulmonary relapse diagnosed by CT 13 months after orchiectomy, he received three cycles of salvage BEP and died of a pulmonary distress syndrome 4 weeks after the last chemotherapy cycle. Autopsy showed no signs of active cancer. Three patients (7.5%) had a metachronous contralateral testicular tumor. Of these, one had a contralateral CS IIA NSGCT with EC >50% and immature teratoma 18 months after initial surgery. He received three additional cycles of BEP, with no further relapse after 206 months. A second patient had a contralateral CS I NSGCT (EC + teratoma) 42 months after orchiectomy. He received three BEP cycles for retroperitoneal relapse after 3 months surveillance, and showed a complete response. Nevertheless, 92 months after the second chemotherapy he developed Philadelphia-positive acute lymphoblastic leukemia (Phi⁺ ALL) and was treated with chemotherapy, autologous and allogeneic stem-cell transplantation, showing no evidence of either cancer 67 months after leukemia diagnosis. The third patient presented 124 months after initial orchiectomy with a second CS IIC NSGCT (EC 65%, seminoma 35%), and was treated with three BEP cycles. Histology of the post-chemotherapy RPLND showed necrotic tumor and he remained relapse free for another 61 more months.

A second malignancy was registered in three patients (7.5%) during follow-up. In addition to the aforementioned patient with leukemia, two other patients were diagnosed with colorectal cancer. Both of them remain relapse-free after standard multimodal treatment of these cancers, 119 and 53 months after colorectal surgery, respectively.

Chemotherapy side-effects: one patient had grade 2 peripheral polyneuropathy after three additional BEP cycles due to contralateral NSGCT CS IIA with EC >50% and immature teratoma. Intermittent grade 1 tinnitus was reported in two patients (5%) and one patient had grade 2 tinnitus (2.5%).

The patient diagnosed with (Phi⁺ ALL) had an estimated glomerular filtration rate of 53 ml/min/1.73 m² and a non-ST elevation myocardial infarction at 210 months of follow-up. No overt nephrotoxicity, cardiotoxicity, or pulmonary toxicity was registered in the other patients.

discussion

relapse rate

After a median follow-up of 15 years, the relapse rate for our 40 high-risk patients after one BEP cycle remains 2.5%, as reported previously [18].

Our results match those of similar studies [11, 12, 15–18] (Table 1). Albers et al. prospectively compared one cycle of adjuvant BEP chemotherapy with RPLND for CS I NSGCT patients [16]. However, only 43% of their patients had high-risk features (VI). Two of 119 patients undergoing chemotherapy relapsed and 15 after undergoing surgery; the 2-year recurrence-free survival rates were 99.5% and 92%, respectively. In the SWENOTECA study, 745 patients received active surveillance or one to two BEP cycles, depending on presence or absence of VI and patient preference [12]. After a median follow-up of 4.7 years, the high-risk chemotherapy group (VI+) had a 3.2% relapse rate versus 41.7% in the surveillance group. These results

Table 1. Published and actual series of 1 cycle of adjuvant cisplatin-based chemotherapy with various definitions for patients with high-risk clinical stage I NSGCT

Author	No. of patients	Treatment	Risk factors	Median f-up (months)	Relapse	Contralateral tumor	Death
Oliver et al. [11]	46	B(60) O(4) P(200) ×1	VI, YS (-), UE, MT	83.5	3	1	1
Gilbert et al. [17]	22	B(90) E(360) P(100) ×1 Carbo E(360) B(90) ×1	VI, YS (-), UE	120	1	0	0
Albers et al. [16]	191	B(90) E(500) P(100) ×1	(43% VI)	56	2	0	0
Tandstad et al. [12, 15]	258	B(90) E(500) P(100) ×1	VI	95	8	0	1
Actual series	40	B(60) E(360) P(120) ×1	VI, EC	186	1	3	1
Total	557				15 (2.7%)	4 (0.7%)	3 (0.5%)

VI, vascular invasion; YS, yolk sac; UE, undifferentiated elements; EC, embryonal cell carcinoma; MT, malignant teratoma.

confirm the high relapse risk in patients with high-risk features and the benefit from adjuvant therapy. Recently, updated results from this study after a median follow-up of 7.9 years showed still the same relapse rate of 3.2% in the group of VI+ patients [15].

RPLND is still the best staging procedure to detect nodal micrometastases. Nevertheless, in 292 NSGCT CS I patients undergoing RPLND, Donohue and Hermans observed a 20%–29% relapse rate even in patients with pathological stage I and EC and/or VI in the orchiectomy specimen after a minimum follow-up of 2 years [2].

contralateral testicular cancer

Testicular cancer survivors (TCS) are at elevated risk of developing a contralateral tumor. With long-term follow-up series becoming available, the incidence increases from 1.9% to 5.2% [14]. Zequi et al. reported a mean time of 68 months to contralateral tumor diagnosis [22]. After a median follow-up of 96 months we previously reported two cases, after 186 months we now add one more.

secondary malignancies

Long-term TCS have a 65%–90% higher risk of developing secondary malignancies than age-matched controls. In 12 691 long-term TCS, Fung et al. found an increased risk of solid malignancies after chemotherapy, radiotherapy, and combined chemoradiotherapy [23] when compared with RPLND only. In 7301 long-term TCS after NSGCT treatment, Chamie et al. reported a higher secondary malignancy risk in patients aged >45 years [24]. However, patients treated with RPLND possibly had predominantly low-stage NSGCT, whereas patients with advanced disease received multiple chemotherapy courses.

Several studies show a 0.5%–1% risk of hematologic malignancies associated with higher doses of etoposide [25]. However, Phi⁺ ALL seen in our patient, is not a typical etoposide-induced leukemia, in contrast to acute myeloblastic leukemia with 11q23 abnormalities.

long-term toxicity

Pulmonary toxicity is a well-known effect of bleomycin, presenting as pneumonitis, and pulmonary fibrosis possibly fatal in

1%–3% of patients given high i.v. doses (>300 000 IU) [26]. We therefore administered bleomycin over 24 h.

The risk of cardiovascular disease is also increased after BEP. In 990 long-term TCS treated with BEP, myocardial infarction risk was increased 3.1-fold compared with a normal matched population, and coronary artery disease risk was increased 5.7-fold compared with RPLND [27]. However, most of the BEP patients had disease stage ≥II and received ≥3 BEP cycles while the majority of RPLND patients had stage I. Our patient with myocardial infarction was a heavy smoker and received treatment of ALL; hence, BEP is an unlikely cause for his cardiac event.

Patients receiving ≤4 BEP cycles have a 28%, those receiving ≥5 cycles a 46% rate of peripheral neuropathy and persistent ototoxic symptoms occur in 5%–65% [26–28]. In our group, only one patient given three additional BEP cycles had grade 2 peripheral neuropathy, and only three patients had tinnitus (grade 1–2).

risk-adapted treatment

Risk-adapted adjuvant chemotherapy may reduce the total number of BEP cycles needed to treat relapse after surveillance [1, 29]. Theoretically, in 100 CS I NSGCT patients undergoing active surveillance, at least 90 BEP cycles would be needed to treat relapses. In our strategy, only 50 high-risk patients would receive one adjuvant BEP cycle and nine cycles are necessary to treat the 3% of patients who still relapse. Thus, our risk-adapted approach requires less chemotherapy and reduces the number of patients requiring multiple cycles.

Approximately 80% (pN₀) of low-risk patients are overtreated by primary RPLND [2]. They require regular follow-up, because some will inevitably relapse. Conversely, if RPLND is restricted to high-risk patients, overtreatment is reduced, but at the price of a higher recurrence rate. Recurrence rates range from 24% to 36% in high-risk CS I NSGCT patients with pathological stage II after RPLND without adjuvant chemotherapy [2]. These patients usually receive two adjuvant BEP cycles to reduce recurrence risk [3]. Thus, in 100 high-risk CS I NSGCT patients undergoing RPLND, ~50 will have positive nodes and hence receive 100 cycles of adjuvant BEP. Of the 50 high-risk patients with negative nodes, up to 15 may still relapse, and need another 45–60 cycles [2]. Therefore, giving one BEP cycle to all high-risk CS I NSGCT

patients implies less chemotherapy, a lower relapse rate and no surgical morbidity from RPLND.

A frequent argument against upfront chemotherapy is the possibility of late relapses with poor prognosis. However, no CS I NSGCT patients have been reported with chemoresistant relapse after one cycle of adjuvant BEP [30].

This study's main strength is its prospective design and long follow-up of 15 years, the longest reported for a similar cohort. Our patients had well-defined risk factors for relapse and met the criteria for high-risk CS I NSGCT (VI and/or EC >50%).

We recommend that active surveillance be used for low-risk patients and adjuvant BEP for high-risk CS I NSGCT patients. A risk-adapted strategy segregating CS I NSGCT patients into low-risk (surveillance) and high-risk (adjuvant BEP) groups as proposed by EAU and American NCCN guidelines may gain wider acceptance if other centers can confirm our excellent results with one modified-BEP cycle for high-risk CS I NSGCT patients.

conclusion

Adjuvant chemotherapy with one modified-BEP cycle is an alternative to two BEP cycles for patients with CS I NSGCT at high-risk of relapse. Its major advantage is a significantly lower relapse rate than reported after RPLND. If our promising results are confirmed by other centers, one cycle of adjuvant BEP should become a first-line standard in high-risk CS I NSGCT patients.

disclosure

The authors have declared no conflicts of interest.

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