advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014; 22: 679–687.

19. Patrick D, Cleeland C, Fallowfield L et al. Denosumab or zoledronic acid (ZA) therapy on pain interference and cancer-specific quality of life (CSQoL) in patients with castrate-resistant prostate cancer (CRPC) and bone metastases (BM). J Clin Oncol 2014; 32: abstr 12.
20. Body JJ, Lipton A, Gralow J et al. Effects of denosumab in patients with bone metastases with and without previous bisphosphonate exposure. J Bone Miner Res 2010; 25: 440–446.
21. Fizazi K, Bosserman L, Gao G et al. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. J Urol 2009; 182: 509–515; discussion 515–506.

Annals of Oncology 26: 374–377, 2015
doi:10.1093/annonc/mdu518
Published online 12 November 2014

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

A. D. Vidal[1], G. N. Thalmann[1], E. Karamitopoulou-Diamantis[2], M. F. Fey[3] & U. E. Studer[1]*

[1]*Department of Urology;* [2]*Institute of Pathology;* [3]*Department of Medical Oncology, Inselspital and University of Bern, Bern, Switzerland*

Received 22 July 2014; revised 4 September 2014, 25 September 2014 and 3 October 2014; accepted 7 October 2014

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/m^2 bleomycin as a continuous infusion over 24 h, 120 mg/m^2 etoposide and 40 mg/m^2 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

Correspondence to: Prof. Urs E. Studer, Department of Urology, University Hospital Bern, Inselspital CH-3010 Bern, Switzerland. Tel: +41-31-632-36-21; Fax: +41-31-632-21-80; E-mail: urs.studer@insel.ch

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/m^2 of bleomycin (given as a continuous i.v. infusion over 24 h to decrease the risk of pulmonary side-effects), 120 mg/m^2 of etoposide and 40 mg/m^2 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 m^2 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% (pN_0) 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 NSCGT 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.

references

1. Vergouwe Y, Steyerberg EW, Eijkemans MJ et al. Predictors of occult metastasis in clinical stage I nonseminoma: a systematic review. J Clin Oncol 2003; 21: 4092–4099.
2. Hermans BP, Sweeney CJ, Foster RS et al. Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol 2000; 163(6): 1721–1724.
3. Albers P, Siener R, Kliesch S et al. Risk factors for relapse in clinical stage I. J Clin Oncol 2003; 21(8): 1505–1512.
4. Albers P, Albrecht W, Algaba F et al. EAU Guidelines on testicular cancer: 2011 update. Eur Urol 2011; 60(2): 304–319.
5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Testicular Cancer. Version 1.2012. http://www.nccn.org (10 July 2014, date last accessed).
6. Kollmannsberger C, Moore C, Chi KN et al. Non-risk-adapted surveillance for patients with stage I nonseminomatous testicular germ-cell tumors: diminishing treatment-related morbidity while maintaining efficacy. Ann Oncol 2010; 21(6): 1296–1301.
7. Cullen MH, Stenning SP, Parkinson MC et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. J Clin Oncol 1996; 14(4): 1106–1113.
8. Pont J, Albrecht W, Postner G et al. Adjuvant chemotherapy for high-risk clinical stage I nonseminomatous testicular germ cell cancer: long-term results of a prospective trial. J Clin Oncol 1996; 14(2): 441–448.
9. Bohlen D, Borner M, Sonntag RW et al. Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. J Urol 1999; 161(4): 1148–1152.
10. Chevreau C, Mazerolles C, Soulié M et al. Long-term efficacy of two cycles of BEP regimen in high-risk stage I nonseminomatous testicular germ cell tumors with embryonal carcinoma and/or vascular invasion. Eur Urol 2004; 46(2): 209–214.
11. Oliver RT, Ong J, Shamash J et al. Long-term follow-up of Anglian Germ Cell Cancer Group surveillance versus patients with Stage 1 nonseminoma treated with adjuvant chemotherapy. Urology 2004; 63(3): 556–561.
12. Tandstad T, Dahl O, Cohn-Cedermark G et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol 2009; 27(13): 2122–2128.
13. Bamias A, Aravantinos G, Kastriotis I et al. Report of the long-term efficacy of two cycles of adjuvant bleomycin/etoposide/cisplatin in patients with stage I testicular nonseminomatous germ-cell tumors (NSGCT): a risk adapted protocol of the Hellenic Cooperative Oncology Group. Urol Oncol 2011; 29(2): 189–193.
14. Abouassaly R, Fossa SD, Giwercman A et al. Sequelae of treatment in long-term survivors of testis cancer. Eur Urol 2011; 60(3): 516–526.
15. Tandstad T, Ståhl O, Håkansson U et al. One course of adjuvant BEP in clinical stage I nonseminoma mature and expanded results from the SWENOTECA group. Ann Oncol 2014; 25(11): 2167–2172.
16. Albers P, Siener R, Krege S et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I nonseminomatous testicular germ cell tumors: AUO Trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol 2008; 26(18): 2966–2972.
17. Gilbert DC, Norman AR, Nicholl J et al. Treating stage I nonseminomatous germ cell tumours with a single cycle of chemotherapy. BJU Int 2006; 98(1): 67–69.
18. Westermann DH, Schefer H, Thalmann GN et al. Long-term followup results of 1 cycle of adjuvant bleomycin, etoposide and cisplatin chemotherapy for high risk clinical stage I nonseminomatous germ cell tumors of the testis. J Urol 2008; 179 (1): 163–166.
19. WHO Histological Classification of Testis Tumours. In Eble JN, Sauter G, Epstein JI, Sesterhenn IA (eds), Pathology & Genetics: Tumours of the Urinary System and Male Genital Organs. Lyons: IARC Press 2004; 218, 250–262, EBM III.
20. Sobin LH, Gospodariwicz M, Wittekind C (eds). TNM Classification of Malignant Tumors. UICC. International Union Against Cancer, 7th edition. Oxford: Wiley-Blackwell 2009; 249–254.
21. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (10 July 2014, date last accessed).
22. Zequi S de C, da Costa WH, Santana TB et al. Bilateral testicular germ cell tumours: a systematic review. BJU Int 2012; 110(8): 1102–1109.
23. Fung C, Fossa SD, Milano MT et al. Solid tumors after chemotherapy of surgery for testicular nonseminoma: a population-based study. J Clin Oncol 2013; 31: 3807–3814.
24. Chamie K, Kurzrock EA, Evans CP et al. Secondary malignancies among nonseminomatous germ cell tumor cancer survivors. Cancer 2011; 117(18): 4219–4230.
25. Westermann DH, Studer UE. High-risk clinical stage I nonseminomatous germ cell tumors: the case for chemotherapy. World J Urol 2009; 27: 455–461.
26. Haugnes HS, Bosl GJ, Boer H et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol 2012; 30: 3752–3763.
27. Haugnes HS, Wethal T, Aass N et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 2010; 28: 4649–4657.
28. Brydøy M, Oldenburg J, Klepp O et al. Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst 2009; 101: 1682–1695.
29. Groll RJ, Warde P, Jewett MA. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol 2007; 64(3): 182–197.
30. Ronnen EA, Kondagunta GV, Bacik J et al. Incidence of late-relapse germ cell tumor and outcome to salvage chemotherapy. J Clin Oncol 2005; 23(28): 6999–7004.