Two Cycles of Cisplatin-Based Chemotherapy for Low-Volume Stage II Seminoma: Results of a Retrospective, Single-Center Case Series

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Key Words

Seminoma • Chemotherapy • Second malignancy

Abstract

Background: To report on the oncological outcome and toxicity of patients treated with 2 cycles of cisplatin-based chemotherapy for low-volume metastatic stage II seminoma.

Methods: We retrospectively identified a case series of 15 patients with seminoma stage IIA (26.7%) and IIB (73.3%) who underwent chemotherapy consisting of 2 cycles of cisplatin, etoposide and bleomycin (PEB) (cisplatin 20 mg/m² on days 1–5, etoposide 100 mg/m² on days 1–5, bleomycin 30 mg on days 1, 8 and 15) according to patient preference (refusing a 3rd cycle of PEB) or institutional practice in the last decades. Complete staging before chemotherapy was available in all patients. Patient age, the side and diameter of the primary tumor, the size of the lymph nodes before and after chemotherapy, acute and late toxicity of chemotherapy, the incidence of second malignancies, the relapse-free rate and cancer-specific mortality were recorded. **Results:** Chemotherapy was well tolerated and no episode of febrile neutropenia occurred. Thrombocytopenia grade 4 was not seen in any patient, while leukopenia grade 4 was observed in 4 (26.6%) patients. The mean (range) lymph node size decreased significantly from 2.54 cm (1.1–4.0) before chemo-

therapy to 0.75 cm (0.4–2.2) after chemotherapy ($p < 0.001$). After a median (range) follow-up of 60 (13–185) months, no patient had relapsed, no patient had died as a result of seminoma and second malignancy was seen in only 1 (6.6%) patient. **Conclusions:** These excellent long-term results from a retrospective case series of 2 cycles of PEB in stage IIA/IIB seminoma patients represent a hint for further research with a view to reducing treatment burden. However, these incidental findings should be studied in prospective trials prior to drawing any conclusions.

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Introduction

Indications for radiotherapy and/or chemotherapy in stage II testicular seminoma are still under debate [1]. There have been efforts to find alternative therapeutic strategies to radiotherapy with similar oncological long-term efficacy for stage II seminoma in order to avoid second primary malignancies as one of the possible late side effects associated with radiotherapy [2]. Regarding the published EAU Guidelines on Testicular Cancer 2011, radiotherapy is considered the standard treatment approach in low-volume metastatic seminoma with a radiation dose of 30 Gy (stage IIA) or 36 Gy (stage IIB) and an

Table 1. Characteristics of patients receiving 2 cycles of chemotherapy following the PEB scheme for stage IIA/IIB seminoma

Factors	Total
Number of patients	15
Mean age, years	39 [21–50]
Tumor	
Right side	6/15 (40.0)
Left side	8/15 (53.3)
Primary tumor diameter, cm	5.0 [3.0–12.0]
pT1	10/15 (66.6)
pT2	4/15 (26.7)
Primary extragonadal (retroperitoneal) seminoma	1/15 (6.7)
Lymph node size, cm	
Before chemotherapy	2.45 [1.1–4.0]
After chemotherapy	0.75 [0.4–2.2]
Thrombocytes, G/l	103,000 [39,000–198,000]
Hemoglobin, g/l	10.3 [6.6–13.6]
Leukocytes, G/l	1,900 [700–4,700]
Anemia grade IV	0/15
Thrombocytopenia grade IV	0/15
Leukopenia grade IV	4/15 (26.6)
AFP level, ug/l	3 [1–8]
hCG level, U/l	2 [0–42]
LDH level, U/l	213 [129–2,228]
Laparoscopic RPLND	2/15 (13.3)
Secondary malignancy	1/15 (6.6)
Recurrence	0/15
Cancer-specific mortality	0/15
Follow up, months	60 [13–185]

Data are presented as n (%) or mean [range].

extended radiation field from the para-aortic region to the ipsilateral iliac field [3]. On the other hand, 4 cycles of etoposide and cisplatin or 3 cycles of cisplatin, etoposide and bleomycin (PEB) have been shown to be highly effective and well tolerated in patients with stage IIA or IIB seminoma with a 5-year progression-free survival of 100% (stage IIA) and 87% (stage IIB) similar to radiotherapy [4]. Unfortunately, cisplatin-based chemotherapy is also associated with dose-depending long-term side effects like peripheral neuropathy and Raynaud phenomenon (RP) as well as gonadal damage in approximately 20–30% of patients following standard-dose therapy [5, 6]. In addition, cisplatin-induced nephrotoxicity and ototoxicity is one of the most dose-limiting side effects, although different studies have identified nephroprotectant (Celecoxib) and otoprotectant (acetyl L-carnitine) drugs for clinical use [7, 8]. To date, no significant increased risk for secondary solid tumors has been ob-

served after chemotherapy [9]; in contrast, therapy-related leukemia and secondary myelodysplastic syndrome are predominantly associated with chemotherapy, particularly with the use of high doses of topoisomerase-II inhibitors and alkylating agents [5]. Due to a higher relative risk of second cancers (1.8) when performing more than 4 cycles of chemotherapy [10], and promising data from nonseminoma patients treated by 2 cycles of cisplatin-based chemotherapy only [11, 12], alternatives to standard therapy with similar oncological efficacy but less toxicity and an improved quality of life could be an attractive treatment option in patients with low-volume metastatic seminoma. To find some real-life evidence for this approach, we performed a retrospective data search among patients treated in our department in the last decades for low volume retroperitoneal stage II seminoma, who had received not more than 2 cycles of PEB.

To our best knowledge, this is the first report of the oncological outcome of 2 cycles of cisplatin-based chemotherapy as a definitive treatment in low-volume metastatic stage IIA and IIB seminoma.

Materials and Methods

Reviewing several charts from testicular cancer patients treated in our department, we identified a case series of 15 patients with low-volume retroperitoneal clinical stage IIA/B seminoma (retroperitoneal mass of <5 cm in diameter) treated between 1996 and 2005 by only 2 cycles of PEB (cisplatin 20 mg/m² on days 1–5, etoposide 100 mg/m² on days 1–5 and bleomycin 30 mg on days 1, 8 and 15; 1 cycle = 21 days) according to patient preference (they refused a 3rd cycle of PEB) or institutional practice (based on data from NSGCT patients treated with 2 cycles of cisplatin-based chemotherapy [11]). After positive approval from the local ethics committee (study number UN3713;279/4.20), these records were retrospectively reviewed for tumor data, treatment, side effects and follow-up data.

Complete staging according to the EAU guidelines 2011 [3] including bilateral testis ultrasound, abdominopelvic and chest CT scan, determination of serum tumor markers like β human chorionic gonadotropin (β hCG, normal levels <10 mU/ml), α -fetoprotein (AFP, normal levels <10 ng/ml) and lactate dehydrogenase (LDH, normal levels <240 U/l) before and after chemotherapy was available in all identified patients.

Six to seven weeks after completing chemotherapy, chest and abdominopelvic CT had been repeated in all patients and the size of the lymph nodes could be compared to that on prechemotherapeutic CT. Other variables were also assessed, like patient age, the side of the primary tumor, histology, diameter of primary tumor, value of thrombocytes, hemoglobin and leukocytes during chemotherapy, the incidence of secondary malignancy, relapse-free rates, cancer-specific mortality and retroperitoneal lymph node dissection (RPLND) ultimately performed on oncological follow-up. Table 1 represents an overview of all evaluated patients' characteristics.

All patients underwent regular follow-up visits at 3-month intervals during the first 3 years, then every 6 months until the 5th year and annually thereafter. Every follow-up visit included a physical examination, a complete blood test including tumor markers (β hCG, AFP and LDH) and imaging with chest and abdominopelvic CT (at every 3rd visit) or abdominal ultrasonography combined with chest X-ray.

Statistical analysis was carried out by descriptive statistics, the Mann-Whitney U test, the χ^2 , the Fisher exact test and the Student t test. A statistical significance was assumed at $p < 0.05$.

Results

A case series of 15 adults with a mean age of 39 (range 21–50) years was identified. All patients had been treated for low-volume metastatic stage II seminoma with 2 cycles of PEB. Four (26.7%) patients had stage IIA disease and 11 (73.3%) had stage IIB seminoma. In 14 (93.3%) patients, pure testicular seminoma was histologically confirmed with pT1 and pT2 category in 10 (66.6%) and 4 (26.7%) patients, respectively, while 1 (6.7%) presented with primary biopsy-proven extragonadal (retroperitoneal) seminoma. The mean (range) diameter of primary testicular tumor measured 5.0 (3.0–12.0) cm. Contralateral double testicular biopsies during orchiectomy performed in 11 (93.4%) patients did not show any testicular intraepithelial neoplasia or synchronous testicular tumor.

Tumor markers were analyzed in all patients before chemotherapy: the mean (range) AFP level was 3 (1–8) μ g/l, β hCG level 2 (0–42) U/l and LDH level 213 (129–2,228) U/l. After chemotherapy, tumor markers were within normal ranges. During chemotherapy, acute toxicity was acceptable and was well tolerated in all patients. No patient developed febrile neutropenia. The mean nadir (range) of leukocytes, thrombocytes and hemoglobin during chemotherapy was 1,900 (700–4,700) G/l, 103,000 (39,000–198,000) G/l and 10.3 (6.6–13.6) g/l. Melanoma (on the thigh) as a secondary malignancy was diagnosed in 1 (6.6%) patient at a routine follow-up 10 years after chemotherapy. This patient underwent melanoma extirpation followed by localized radiotherapy; the 5-year relapse-free rate remained 100%.

The mean (range) lymph node size decreased significantly from 2.54 (1.1–4.0) to 0.75 (0.4–2.2) cm before and after chemotherapy ($p < 0.001$). Six weeks after chemotherapy, 2 (13.3%) patients had undergone laparoscopic retroperitoneal lymph node dissection to assess for residual active tumor because of incomplete remission (residual masses after chemotherapy of 2.2 and 1.5 cm, re-

spectively). No active tumor specimen was confirmed on complete histological evaluation, and necrosis/sclerosis in lymphatic tissue was found in both patients. A unilateral template without preservation of postganglionic nerve fibers on the affected side was carried out, antegrade ejaculation was preserved and both patients fathered a healthy child during follow-up. In the remaining 13 (86.7%) patients, the diameter of lymph nodes was <1.5 cm after chemotherapy and those patients have been followed up.

After a median (range) postchemotherapy follow-up of 60 (13–185) months, all patients remained recurrence-free and the cancer-specific mortality was 0%.

Discussion

Testicular seminoma accounts for approximately 50% of all germ cell testicular tumors. The majority of patients have stage I disease [13] and a cure is achieved in approximately 100% of cases, whatever treatment strategy is applied (adjuvant radiotherapy, adjuvant chemotherapy or surveillance) [14]. In contrast, only 20% of seminoma patients present with low-volume or even advanced metastatic disease [13]. So far, radiotherapy is the treatment of choice for stage IIA/B seminoma with an excellent cause-specific survival of 95% after 20 years [2] and a relapse-free survival of 95.3% (stage IIA) and 88.9% (stage IIB) after 6 years [15].

Regarding the high incidence of second malignancies (approx. 9% after 13 years) after more than 2 decades after radiotherapy (especially in cancers of the stomach, bladder and possibly pancreas) [16, 17], more clinical trials are focusing on reducing toxicity while maintaining oncological efficacy as well as exploring new salvage strategies with improved cure and survival rates [18]. In the trial of Bachaud et al. [19], the cumulative incidence of second non-germ-cell cancers after radiotherapy in stage I–II seminoma was 10.7% after a mean follow-up of 11 years, increased particularly in patients treated by combined infra- and supradiaphragmatic irradiation. While on the one hand, the risk of second malignancy after combined supra- and infradiaphragmatic radiotherapy is elevated, on the other hand, infradiaphragmatic radiotherapy alone is associated with a higher incidence of mediastinal/supraclavicular relapse in patients with stage IIA seminoma (15%) and stage IIB (50%) after a median follow-up of 18 years, suggesting that systemic treatment with chemotherapy could represent a better therapeutic option in this cohort [20].

By contrast, secondary leukemia or lymphoma is predominantly associated with the use of chemotherapy in a dose-depending manner [9]. In our case series, we noticed no case of second hematological tumor as a possible consequence of reduced dose rate performing 2 cycles of cisplatin-based chemotherapy, but the number of patients was very small and the follow-up period of mean 60 months is admittedly way too short to definitively exclude leukemia/lymphoma; during a follow-up of 15 years, the estimated relative risk of leukemia at a cumulative dose of 650 mg cisplatin (commonly administered in current testicular cancer treatment regimens) was 3.2 [21]. Hemminki et al. [22] conducted a study with 5,533 survivors of testicular cancer (seminoma treated with radiotherapy, nonseminoma treated with chemotherapy) to compare late effects between radiotherapy and chemotherapy. In 370 (6.7% of all patients) second cancers were recorded, more of them in radiated seminoma than in chemotherapy-treated nonseminoma patients. Gastrointestinal tract cancers also dominated after seminoma treatment, while bladder cancers occurred more often in nonseminoma survivors. In our retrospective case series, the incidence of secondary malignancy was similar, 1 (6.6%) patient developed melanoma (10 years after primary chemotherapy), which in our opinion is not a typical therapy-related secondary malignancy after testicular cancer treatment.

Reducing chemotherapy may have a significant impact on a patient's life due to: firstly, acute toxicity of 2 cycles of PEB is significantly less after 2 PEB cycles than after 3 or 4 [23], secondly, the cumulative dose and serum levels of cisplatin and etoposide are the major predictor for acute and late toxicity like leukemia, Leydig cell insufficiency, alteration of gonadotropin levels, oto- and neurotoxicity [24] and thirdly, increasing knowledge is gained on elevated cardiovascular risk profile after standard-dose chemotherapy [12]. The fact that cisplatin-based chemotherapy had been reduced to 2 cycles in these 15 patients might indeed have positively influenced short- and long-term toxicity and thereby also increased their quality of life – still maintaining encouraging oncological results (no relapse, no cancer-related mortality and no cardiovascular disease at a median of 60 months after chemotherapy) similar to radiotherapy. Acute toxicity during chemotherapy was acceptable, anemia and thrombocytopenia grade 4 were not seen in any patient, while leukopenia grade 4 was observed in 4 (26.6%) patients. No episode of febrile neutropenia was documented. Because most major cardiac and second malignancy events happen more than 20 years after radiotherapy, a focus must

be made on the importance of regular long-term follow-up [20].

Although many authors advocate chemotherapy as a primary treatment only in patients with advanced clinical stage IIC, III and IV disease [25, 26], Ceccaldi et al. [27] reported a remission rate of 100% in patients with stage IIA and IIB seminoma after 3 courses of BEP (bleomycin, etoposide, platinum) chemotherapy; they recommend treating patients with orchiectomy in addition to chemotherapy and not with more toxic radiotherapy. These results were confirmed by Garcia-del-Muro et al. [4], who assigned 72 patients with pure seminoma to 4 cycles of cisplatin/etoposide or 3 PEB cycles with an overall 5-year progression-free and overall survival rate of 90 and 95%, respectively, at a median follow-up of 71.5 months. Giannis et al. [28] also concluded that patients with low-volume metastatic stage IIA and IIB seminoma can be treated by 4 cycles of PEB instead of radiotherapy with the risk of diverse toxicity effect. A different chemotherapy strategy was studied by Krege et al. [29], investigating the use of single-agent carboplatin at a dose of AUC 7 in 108 patients with seminoma stages IIA (3 cycles) and IIB (4 cycles). Complete response, partial response, no response and progressive disease were displayed in 81, 16, 2 and 1%, prospectively. Therefore, single-agent carboplatin chemotherapy (4 cycles) did not sufficiently eliminate retroperitoneal metastases and was not recommended in stage IIA/IIB seminoma [29]. Combining carboplatin and radiotherapy for seminoma stage IIA/IIB appears to have additional toxicity, but reduces the relapse rate on long-term follow-up with a 5-year relapse-free survival of 92.3% (stage IIA) and 100% (stage IIB) compared to radiotherapy alone (5-year relapse-free survival of 84.9% in stage IIA and 69.4% in stage IIB) [30]. Even though a combined therapy (radiotherapy and chemotherapy) seems to scale the relapse rate, we should bear in mind that the relative risk (2.9) of a second cancer (especially hematological malignancy) is increased by implementing both of them in the same patient; therefore, this combination should be avoided [10, 31].

In the treatment of metastatic testicular seminoma, a variety of current studies (publ. between 2002 and 2011) confirm that only patients with residual retroperitoneal masses >3 cm in diameter or PET-scan-positive patients should be considered for surgery (RPLND), while patients with masses <3 cm should undergo surveillance with close observation [18, 28, 32]. As most of the patients in our study were treated before that time, laparoscopic RPLND was performed in 2 patients (in 1999 and 2002) 6 weeks after chemotherapy with residual masses <3 cm

(but >1.5 cm) according to institutional practice at that time. Since the SEMPET trial by De Santis et al. [33], this is no longer common practice. Despite being aware of possible severe complications of postchemotherapy laparoscopic RPLND, surgery was completed in both patients successfully due to our experience [34]; no active tumor was detected in any RPLND specimen (sclerosis on histological evaluation) and antegrade ejaculation was preserved in both patients. Regarding the EAU Guidelines on Testicular Cancer 2011 [3], FDG-PET should be performed in patients with residuals of >3 cm, while in patients with residuals of <3 cm, the use of PET-scan is optional (based on the results of the prospective multicentric SEMPET trial [33]). As nearly all patients were treated in an era before the routine use of PET in seminoma patients and all evaluated patients had postchemotherapy residual masses <3 cm, PET scan was not performed in any patient.

The recurrence rate of 2 × PEB (0%) – at an admittedly short median follow-up of 5 years – was similar to

current published results of radiotherapy (recurrence rate: 5% stage IIA and 11% stage IIB after a median observation time of 5.8 years) [15]. This could indicate that administering only 2 cycles of chemotherapy in patients with low-volume metastatic seminoma, instead of 3 or 4, may be a promising therapy alternative. Prospective (and probably multi-institutional) randomized trials with sufficient statistical power and long-term follow-up are necessary to verify in detail the oncologic efficacy and side effects of this possible therapy option (2 × PEB vs. radiotherapy/3 × PEB). The obvious limitation of this case series is the anecdotal sample size of 15 patients retrospectively evaluated with subsequent restricted methods of interpretation of oncological results.

These excellent long-term results from a retrospective case series of 2 cycles of PEB in stage IIA/IIB seminoma patients represent a hint for further research that aims to reduce treatment burden. However, these incidental findings should be studied in prospective trials prior to drawing any conclusions.

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