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Adjuvant bleomycin, etoposide and cisplatin in pathological stage II non-seminomatous testicular cancer: the Indiana University experience

M. Behnia [a], R. Foster [b], L.H. Einhorn [a,*], J. Donohue [b], C.R. Nichols [a]

[a] *Department of Medicine, Division of Hematology-Oncology, Indiana University, Indiana Cancer Pavilion RT 473, 535 Barnhill Drive, Indianapolis, IN 46202-5289, USA*

[b] *Department of Urology, Indiana University Medical Center, Indianapolis, IN, USA*

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Abstract

Two cycles of bleomycin, etoposide, and cisplatin (BEP) were evaluated as adjuvant chemotherapy for patients with pathological stage II non-seminomatous germ cell tumours. Between 1985 and 1995, 86 patients with pathological stage II non-seminomatous testicular cancer were treated with two cycles of BEP. At retroperitoneal lymph node dissection (RPLND) 49 patients (57%) had pathological stage II_A (microscopic nodal metastases) and 37 (43%) had stage II_B (gross nodal metastases). After RPLND, the patients received bleomycin, 30 units weekly for 8 weeks, etoposide (100 mg/m^2) and cisplatin (20 mg/m^2) each for 5 days every 28 days for two cycles as adjuvant chemotherapy. 4 patients were lost to follow-up. 10 patients (12%) developed granulocytopenic fever during their chemotherapy. Of the 82 evaluable patients all remained with no evidence of disease except for a single patient with a cervical nodal relapse of teratoma. This was resected and he remains disease free. Median follow-up has been 85 months (range: 42–173 months). In patients with fully resected stage II non-seminomatous germ cell tumour, two cycles of BEP were almost universally effective in preventing relapse.

Keywords: Testicular cancer; Adjuvant; Bleomycin; Etoposide; Cisplatin

1. Introduction

The history of the use of adjuvant chemotherapy in germ cell tumours seems to validate one of the most important general principles of adjuvant treatment in oncology, i.e. the most effective adjuvant programmes utilise the most effective chemotherapy regimens for metastatic disease. These regimens are applied in an intensive and aggressive schedule. The concept of diminished dose, single agent or intermittently scheduled adjuvant chemotherapy is largely outdated [1].

In non-seminomatous germ cell cancer, early studies utilised available single agents such as chlorambucil or actinomycin-D as prolonged intermittent treatment after full resection of the primary tumour [2]. Whilst these regimens were probably partly effective in reducing relapse, it was not until the development of more effective therapy for metastatic disease (cisplatin-based treatments) that adjuvant therapy became universally successful [3]. As reported in the Testis Intergroup Study in 1987, two cycles of cisplatin, vinblastine and bleomycin (PVB) or vinblastine, actinomycin-D, cyclophosphamide, cisplatin and bleomycin (VAB-6) were almost completely effective in preventing relapse [4].

At the same time that the efficacy of adjuvant cisplatin, vinblastine, bleomycin-based regimens was being demonstrated, the role of etoposide in primary treatment of metastatic disease was being evaluated. Etoposide was less toxic than vinblastine and in advanced disease, more effective. Etoposide has replaced vinblastine in virtually all first-line regimens for metastatic germ cell tumours [5,6].

There has been a *de facto* acceptance of the efficacy of etoposide-based regimens as adjuvant treatment of resected stage II non-seminoma. At our institution, two cycles of bleomycin, etoposide and cisplatin has become standard adjuvant therapy for those patients electing additional treatment after full surgical resection. In

* Corresponding author. Tel.: +1-317-274-0920; fax: +1-317-274-3646.

E-mail address: leinhorn@iupui.edu (L.H. Einhorn).

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order to support this assumption of efficacy and safety, we report our results of two cycles of BEP in such patients treated since 1985. We retrospectively reviewed all patients who had surgery at Indiana University, had positive nodes, and elected to be treated with adjuvant BEP.

2. Patients and method

From 1985 through 1995, 86 consecutive patients with pathological stage II non-seminomatous germ cell tumour (NSGCT) who received adjuvant BEP were reviewed. At Indiana University, all patients with clinical stage II NSGCT and less than 3 cm maximal transverse diameter of abdominal nodes underwent a retroperitoneal lymph node dissection (RPLND). In addition, the great majority of patients with clinical stage I NSGCT also underwent a RPLND. The decision to receive or not receive adjuvant chemotherapy was largely a personal decision of the patient and his family. Patients were counselled about their RPLND pathology concerning probability for cure with surgery alone. It was anticipated that adjuvant BEP would largely eliminate probability for relapse. Patients were then explained the benefits of adjuvant chemotherapy versus the expected toxicity. They were also told that with appropriate follow-up, it was anticipated that equivalent overall survival would be achieved, but would require closer follow-up and longer duration of chemotherapy if metastases developed. Eligibility included resection of the primary testicular tumour, followed by RPLND at Indiana University and evidence of nodal involvement by pathological analysis. The American Joint Committee on Cancer (AJCC) TNM staging for germ cell tumours was utilised for pathological staging purposes: stage II_A is involvement of 5 or less than 5 nodes, none more than 2 cm in size and with no extranodal extension. Stage II_B is involvement of more than 5 nodes and/or nodes greater than 2 cm diameter. Preoperative evaluation included a chest X-ray and computed tomography (CT) scan of chest and abdomen, measurement of complete blood count, beta-human chorionic gonadotropin (BHCG) and alphafetoprotein (AFP) levels. Prior to initiation of adjuvant chemotherapy, markers and chest X-ray were required to be normal. Routine pulmonary function tests were not performed as low cumulative doses of bleomycin (240 units) were being used.

The doses of chemotherapeutic agents were as follows: (a) cisplatin 20 mg/m^2 intravenously and etoposide 100 mg/m^2 intravenously on days 1–5. Cycles were repeated every 28 days; (b) bleomycin at 30 IU/week for 8 weeks. Standard techniques of hydration and antiemetic management were used. Bleomycin toxicity was monitored on clinical grounds by careful physical examination of the chest, assessing for inspiratory rates or respiratory lag.

Long-term follow up after the completion of chemotherapy was done by frequent measurement of serum markers, physical exam and a chest radiograph for 2 years and this diminished to an annual basis by the third year.

3. Results

86 patients with stage B non-seminomatous germ cell tumour were studied in this report. The characteristics of patients are listed in Table 1. 49 patients (57%) had pathological stage II_A and 37 (43%) had pathological stage II_B.

Two cycles of cisplatin, etoposide and bleomycin were administered to all patients except the following ($n = 81$, 94%): 4 patients received three cycles of the regimen and 1 patient refused further chemotherapy after the first cycle.

10 patients (12%) developed neutropenic fever during treatment. One developed moderate mucositis and another developed a syncopal episode with the second cycle of BEP. No clinically significant bleomycin-related lung toxicity was observed. There were no chemotherapy-related deaths.

4 of the 86 patients (5%) were lost to follow-up, at which time they were disease-free. 3 of these 4 patients were 3–5 years postcompletion of adjuvant BEP. The other patient was from South America, and several months after completion of adjuvant BEP, we received no further information concerning this case. 3 patients developed a second primary testicular tumour: embryonal cell carcinoma (1), Leydig cell tumour (1), and a second seminoma (1). Fertility was not assessed. One patient relapsed with a solitary cervical nodal metastasis with normal serum markers. This was completely resected and revealed only mature teratoma, and this patient has remained disease free with no subsequent therapy. All other patients have remained continuously disease free with minimal follow-up of 42 months from initiation of adjuvant BEP. The median follow-up was 85 months (range: 42–173).

Table 1
Patient characteristics

Characteristic	*n* (%)
Preoperative clinical stage	
I	45 (52)
II_A	29 (34)
II_B	12 (14)
Pathological stage	
II_A	49 (57)
II_B	37 (43)

4. Discussion

The results of our retrospective review confirmed the value of two courses of adjuvant BEP. Two cycles of adjuvant BEP reliably prevented relapse of malignant germ cell tumour in this large group of consecutive patients electing adjuvant therapy after full resection of non-seminomatous germ cell tumour. The short-term toxicity was manageable with no therapy-related deaths, a low incidence of granulocytopenic fever and negligible pulmonary or mucocutaneous toxicity. The retrospective nature of the study precluded physiological assessment of pulmonary functions, but by all clinical parameters there was no clinically significant pulmonary toxicity. There has been concern that etoposide is leukaemogenic and perhaps should not be used as adjuvant chemotherapy. However, this was dose-dependent and studies from our centre demonstrated a less than 1% incidence of leukaemia in treatment of metastatic disease with etoposide [7].

To a large degree, our outcome mirrors the results of the Testis Intergroup Study [4]. In the trial, two cycles of cisplatin-based chemotherapy (PVB or VAB-6) largely prevented relapse, was well tolerated and was associated with no long-term toxicities. The results of this trial along with our report herein suggest that two cycles of cisplatin combination chemotherapy will, in essence, prevent relapse in all patients who have been rendered disease free after retroperitoneal lymphadenopathy. A previous study in metastatic disease demonstrated statistically and clinically lesser neurotoxicity with BEP versus PVB [5].

We did not formally assess pulmonary function tests in this group of patients as it was felt that this low cumulative dose of bleomycin (240 units) was unlikely to produce significant toxicity. This hypothesis was supported by other trials with three courses of BEP (270 units of bleomycin) in metastatic disease that also demonstrated an absence of clinically significant pulmonary toxicity [8,9].

Attempts to reduce chemotherapy toxicity in patients with favourable prognosis germ cell tumours are important to consider. In good-risk metastatic disease, serial trials have reduced toxicity whilst retaining efficacy (e.g. the substitution of etoposide for vinblastine [5], the use of EP versus VAB-6 [6], and the documentation of the equivalence of three cycles to four cycles of BEP [9]. However, some attempts to reduce toxicity have also reduced therapeutic efficacy (e.g. elimination of bleomycin with three courses of BEP [8] or substitution of carboplatin for cisplatin [10–12]. It is unlikely that equally effective, less toxic therapy for good-risk disseminated disease will be found with currently available drugs. The three cycles of BEP or four cycles of EP remain standards of treatment for good-risk metastatic disease [13,14].

A recent study by Motzer and colleagues reports the results of two-drug adjuvant therapy with cisplatin and etoposide and demonstrates that this two-drug combination represents an alternative to BEP. In this trial of 50 patients, all patients have remained free of relapse with a median follow-up of 3 years [15]. Toxicity was primarily confined to myelosuppression (25% of patients experienced granulocytopenic fever). The second course of cisplatin plus etoposide was started on day 22, whereas in our adjuvant BEP series, courses were given every 4 weeks.

We believe our results confirm that adjuvant therapy for fully resected stage II non-seminoma with two cycles of BEP is effective and safe.

Because of very low relapse probability, our guidelines for follow-up following adjuvant chemotherapy are as follows: history and physical examination including palpation of the remaining testis and PA and lateral chest X-ray and markers every 3 months for the first year, every 6 months during the second year and then every 12 months thereafter. It is not necessary to perform CT scans after adjuvant BEP chemotherapy. However, it could be assumed that adjuvant chemotherapy does not apparently protect the contralateral testis from a second primary, as 3 of the 82 patients had a contralateral primary, including 2 with germ cell cancers.

Whilst this report does not represent the result of a randomised comparison with the old standard (cisplatin, vinblastine and bleomycin) the number of studies showing equal or better therapeutic results in metastatic disease gives additional confidence that substitution of etoposide for vinblastine will retain efficacy as adjuvant therapy [5,6]. Further refinements of adjuvant therapy, including additional courses of cisplatin combination chemotherapy, cannot improve therapeutic outcome. Toxicity of current therapy is largely short term and manageable. The strategy following resection of positive retroperitoneal lymph nodes should be either two courses of adjuvant chemotherapy or close observation with institution of chemotherapy if metastases develop.

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