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Original Paper

Carboplatin and Ifosfamide and Selective Consolidation in Advanced Seminoma

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This prospective phase II study assesses the clinical efficacy and complications of a treatment regimen comprising combination chemotherapy with carboplatin and ifosfamide and selective consolidation in advanced seminoma. Of 43 patients who entered the study, between May 1989 and May 1992, 42 were evaluable. 30 achieved a complete remission (71%; 95% confidence interval, 56–84%) after chemotherapy alone. 10 achieved a complete remission (24%; 95% confidence interval, 13–39%) after chemotherapy plus consolidation. 38 of the 42 patients (91%; 95% confidence interval, 83–98%) remained in remission after a median follow-up period of 35 months (20–56 months). No patient experienced nephrotoxic, neurotoxic, or ototoxic effects, or haemorrhagic cystitis. Ten per cent of the patients had leucopenic fever requiring hospitalisation. Twenty-four per cent required platelet transfusions, and 26% required transfusions of packed red blood cells. For patients with seminoma, treatment with carboplatin and ifosfamide and selective consolidation is safe and effective.

Key words: carboplatin, ifosfamide, seminoma
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INTRODUCTION

AT THE University of Texas M.D. Anderson Cancer Center, the treatment protocol for patients with advanced seminoma is different from that for patients with non-seminomatous germ cell tumour. The difference in strategy is based on the seminoma's apparent greater sensitivity to both chemotherapy and radiation therapy, the relative difficulty of surgical resection and unique clinical features.

The different sensitivities to chemotherapy of seminoma and non-seminomatous germ cell tumours were most apparent during the initial development of chemotherapy for germ cell tumours, before the availability of cisplatin. The combination chemotherapy regimen of vinblastine and bleomycin (VB) was effective in a significant proportion of patients with non-seminomatous tumours, but ineffective in patients with seminoma [1]. The major advance in chemotherapy of seminoma came with the incorporation of cisplatin. In the initial reports of the use of cisplatin as a single agent in patients with germ cell tumours, long-term disease-free survival was reported in patients with seminoma, but not in patients with non-seminomatous tumours [2]. The seminomas' apparent increased sensitivity to cisplatin and relative resistance to the VB regimen led us to study cisplatin-based chemotherapy regimens in patients with advanced seminoma. The addition of an alkylating agent to cisplatin for these patients was prompted by the significant antitumour activity of these agents and their reported synergy with cisplatin [3–6].

Besides being more sensitive to cytotoxic chemotherapy than non-seminomatous germ cell tumours, seminoma is known to be more radiation-sensitive [7]. Furthermore, comparison of the two tumour types by surgical resectability of residual masses following chemotherapy highlights an important difference between the two. Whereas the standard practice in non-seminomatous germ cell tumours is elective surgery for residual disease, in seminomas the situation is quite different. Pronounced fibrotic changes make surgery for seminomas much more difficult and complications more frequent. Finally, the metastatic spread of seminomas appears to be more indolent and predictable than that of other germ cell tumours. The therapy of seminoma at the M.D. Anderson Cancer Center has focused on exploiting these differences.

In our initial experience treating seminoma patients with a regimen combining cisplatin and cyclophosphamide and selective consolidation, we concluded that the combination was effective. Ninety-two per cent of the patients had survived, free of disease for long periods [8]. The major side-effects were those attributed to repeated doses of cisplatin, that is, nephrotoxicity,

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neurotoxicity, or ototoxicity. Encouraged by the therapeutic success of that inital trial, we expanded our study to evaluate combinations of cisplatin analogues and alkylating agents in an attempt to find a combination with a similar high cure rate without the relatively high complication rate. The first alternative we evaluated was the combinations of carboplatin and ifosfamide. These two agents were selected because of their individual antitumour activities and their relatively mild toxicity profiles.

PATIENTS AND METHODS

Study population

Patients were enrolled in the study between May 1989 and May 1992. 43 patients with a diagnosis of advanced seminoma were assessed by a review of the tumour hisotogical type; serum tumour marker assays for β-human chorionic gonadotropin (β-HCG), alpha fetoprotein (AFP), and lactate dehydrogenase (LDH); and computed tomographic (CT) scans of the thorax, abdomen, and pelvis. Patients with visceral metastases were further staged by isotope bone scan in addition to a complete blood count with platelet count, electrolytes and assessment of renal and liver function.

42 of the patients met the following criteria and were evaluated in our study. Patients had histological confirmation of a pure seminoma; advanced disease defined as any tumour characterised by any of the following: extragonadal origin, supradiaphragmatic involvement, a retroperitoneal mass more than 10 cm in maximum transverse diameter, visceral disease, or radiation therapy failures. Patients were ineligible if they had an abnormal level of serum AFP (>5 ng/ml) in two measurements 1 week apart. The 1 patient excluded from this study had a histological diagnosis of non-seminomatous germ cell tumour. The 42 patients signed the informed consent approved by the internal review board of the M.D. Anderson Cancer Center.

Treatment

The induction chemotherapy consisted of intravenous carboplatin at a dose of 400 mg/m^2 of body surface area given over a period of 2 h on day 1, followed by intravenous ifosfamide 1.5 g/m^2 of body surface area given over 2 h each day on days 2–5 for a total of 8 h. Dose levels are shown in Table 1. Each dose of ifosfamide was delivered with adequate hydration and simultaneous mesna, 240 mg/m^2 of body surface area injected at 0, 4 and 8 h. All patients were scheduled to receive a minimum of four courses of induction chemotherapy at 28-day intervals. Doses of carboplatin and ifosfamide were modified if indicated by granulocyte counts, platelet counts, or non-haematological toxicity (Table 2).

Statistical analysis

All evaluable patients are included in this analysis. Response duration and survival were measured from the date of initiation of therapy. Survival curves were generated by using the Kaplan–Meier method [9].

Table 1. Dose levels

Level	Carboplatin	Ifosfamide
0 (starting dose)	400 mg/m^2	1.5 g/m^2
−1	325 mg/m^2	1.2 g/m^2
−2	250 mg/m^2	1.0 g/m^2

Table 2. Dose modification criteria

Reduction by one level (−1)
Grade III non-haematological toxicity
Granulocyte nadir <100
Platelet nadir <25
Reduction by two levels (−2)
Grade IV non-haematological toxicity
Organ infection
Severe bleeding

Response criteria

The treatment of advanced seminoma with chemotherapy classically results in a persistent residual mass [10]. Our own experience and that of the Memorial Sloan-Kettering Cancer Center prompted us to adopt the following criteria. Patients were classified as having either a complete remission in response to chemotherapy or a response to chemotherapy that required consolidation. A complete remission to chemotherapy was defined as disappearance of all clinical and biochemical evidence of disease with either complete resolution on radiographic examination, or a stable residual mass less than 3 cm in maximum transverse diameter. A response to chemotherapy requiring consolidation was defined as disappearance of all clinical and biochemical evidence of disease with a persistent stable mass 3 cm or more in maximum transverse diameter. Patients received a minimum of four courses of induction chemotherapy, with an additional requirement of two courses beyond complete remission or prior to consolidation. Patients achieving a complete remission are simply observed. Patients with a persistent stable mass of 3 cm or more in maximum transverse diameter received consolidation consisting of definitive radiation therapy. Fine-needle aspirates were taken before radiation therapy from the residual mass. We planned surgical resection of the residual mass only for those patients with clinical features that led us to suspect the existence of non-seminomatous tumour. Patients were defined in our protocol to be at risk if they had a poor response to chemotherpy or a biomarker response that is not characteristic of a pure seminoma, namely a late rise in the serum AFP level.

RESULTS

Patient characteristics

Clinical features were recorded for the evaluable 42 patients (Table 3). Twenty four per cent of the patients were radiation therapy failures. Seventy-six per cent of the patients presented with a primary testicular tumour, whereas 31% presented with a tumour of extragonadal origin. The extragonadal primary site was the mediastinum for 9 patients, retroperitoneum for 2 patients, and pineal body for 2 patients. Sixty-six per cent of the patients presented with an elevated β-HCG level, with a median value of 17 mlu/ml (normal, ≤3; range, 3.1–8521). Seventy-one per cent of the patients presented with an elevated LDH with a median value of 1183 lu/l (normal, 313–618; range, 657–10 819). Serum AFP was not elevated in any patient, as defined by the eligibility criteria.

Seminoma is commonly characterised by its advanced local complications as was the case with our patients (Table 4). One patient who presented with respiratory failure began treatment while on mechanical ventilation support.

Table 3. Characteristics of the 42 patients with advanced seminoma entered in this study

Characteristic	No. of patients (%)
Performance status, Zubrod	
0	10
1	28
2	3
3	0
4	1
Previous radiation therapy	10 (24)
Primary site	
Testis	29 (69)
Extragonadal	13 (31)
Mediastinum	9
Retroperitoneum	2
Pineal body	2
Elevated serum markers	
β-HCG	32 (76)
LDH	30 (71)
Median age in years (range)	35 (17–69)

Table 4. Disease complications at presentation

Complication	No. of patients (%)
Retroperitoneal pain	15 (36)
Obstructive uropathy	5 (12)
Superior vena cava syndrome	5 (12)
Respiratory failure	4 (10)
Inferior vena cava syndrome	1 (2)
Spinal cord compression	1 (2)
Pericardial invasion	1 (2)

Response and survival

The responses to therapy are outlined in Table 5. Between four and seven (median, five) courses of carboplatin and ifosfamide were delivered to each patient. Of the 42 patients evaluable for response, 30 (71%) achieved a complete remission in response to chemotherapy alone, while another 10 (24%) achieved a complete remission in response to chemotherapy plus consolidation, for an overall 95% complete remission rate. Postchemotherapy consolidation consisted of radiation therapy or surgery. 6 patients, each with a persistent residual mass of 3 or more cm in maximum transverse diameter, received definitive radiation therapy (4 retroperitoneal and 2 in the mediastinum). Prior to definitive radiation therapy, cytological analysis of the residual mass, removed by fine-needle aspiration, revealed no evidence of viable seminoma or non-seminomatous elements. 2 patients with pineal primary tumour received involved field radiation theapy, despite achieving a complete remission to chemotherapy. 2 patients who underwent postchemotherapy retroperitoneal lymph node dissection because of concerns about residual non-seminomatous germ cell tumour, were found to have no evidence of viable seminoma or non-seminomatous elements.

Table 5. Responses to therapy of 42 patients with advanced seminomas

Response	No. of patients (%)
Complete remission, chemotherapy alone	30 (71)
Complete remission, chemotherapy plus consolidation	10 (24)
Treatment failure	2 (5)
Total	42 (100)

The remaining 2 patients did not respond to the combination of carboplatin and ifosfamide. One patient, who presented with an anterior mediastinal mass, developed new pulmonary nodules after four courses of therapy. A postchemotherapy surgical resection revealed a poorly differentiated carcinoma consistent with the re-evaluation of the baseline pathological diagnosis, and in retrospect, did not possess features of seminoma. The patient underwent alternative chemotherapy and subsequently died of his disease. The other patient, who had a clinical stage I seminoma, had a recurrence within the radiation field, with a 2 cm retrocrural node (cytological analysis of fine-needle aspirate was consistent with seminoma) and a β-HCG level of 2263 mlu/ml, received four courses of chemotherapy. The X-ray was normal despite fluctuations in the β-HCG. Within 2 months, the β-HCG level began to rise sharply while the radiographs remained normal. The patient received salvage chemotherapy (bleomycin, etoposide, cisplatin) and achieved a complete remission.

The complete remission rate was durable (Figure 1). 38 of the 42 patients (91%) remained free of disease with a median follow-up period of 35 months. 2 patients who relapsed with seminoma achieved a second complete remission with cisplatin-based salvage chemotherapy. Overal survival is shown in Figure 2. 41 patients (98%) are alive, and disease-free with a median follow-up period of 39 months.

Toxic effects

Toxic effects are summarised in Table 6. There were no treatment-related deaths. Nadir blood counts are summarised in Table 7. No patient experienced deterioration of renal function,

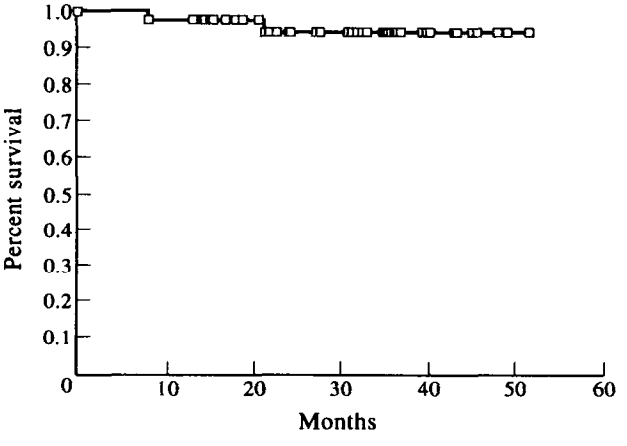

Figure 1. Disease-free survival.

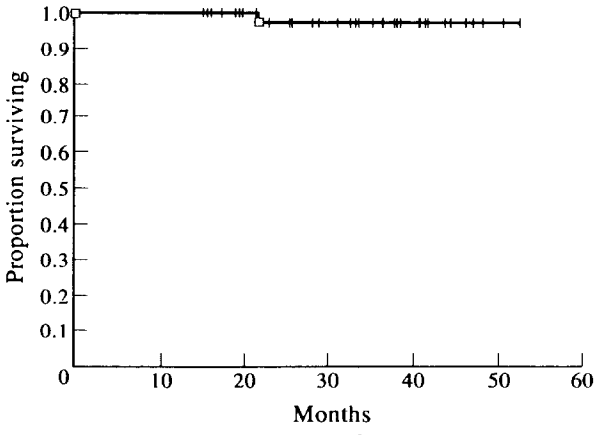

Figure 2. Overall survival.

Table 6. Complications of chemotherapy

Complications	No. of patients (%)
Nephrotoxicity	0 (0)
Neurotoxicity	0 (0)
Ototoxicity	0 (0)
Haemorrhagic cystitis	0 (0)
Leucopenic fever	4 (10)
Platelet transfusions	10 (24)
Packed red blood cells transfusions	11 (26)

Table 7. Nadir blood counts

Course	Leucocytes (cells/mm³) Median (Day) (Range)	Platelets (cells/mm³) Median (Day) (Range)	Haemoglobin (g/dl) Median (Day) (Range)
1	1.3 (14) (0.3–2.9)	100 (17) (7–255)	11.6 (16) (7.4–15)
2	1.9 (12) (0.4–3.6)	92 (18) (20–187)	11.0 (15) (7.3–13.6)
3	1.5 (12) (0.5–3.5)	72 (17) (19–208)	10.1 (17) (7.4–13.0)
4	1.5 (12) (0.2–3.5)	82 (18) (9–236)	10.3 (14) (7.4–13.7)

symptomatic peripheral neuropathy, ototoxic effects or haemorrhagic cystitis. Ten per cent of the patients had leucopenic fever requiring hospitalisation. Twenty-six per cent required transfusions of packed red blood cells because of a haemoglobin level less than 8 g/dl or symptomatic anaemia. Twenty-four per cent required platelet transfusions for a platelet count under 20 cells/mm³ or for symptoms of bleeding. 10 patients (24%) had their chemotherapy doses reduced to dose level −1, and one of those (2%) required an additional dose reduction because of haematological effects. 4 of the patients who had their dose reduced had received previous radiation therapy.

DISCUSSION

Chemotherapy with the combination of carboplatin and ifosfamide and consolidation therapy as needed is a highly effective approach for patients with advanced pure seminoma. Ninety-one per cent of the patients treated with this strategy remained in complete remission after a median follow-up period of 35 months. This follow-up is beyond the risk of failure for the majority of patients with seminoma. Since none of the patients with a residual mass had viable disease at the planned fine-needle aspiration before radiation therapy, we cannot be certain of the contribution of radiation consolidation to these results. The response rate we report compares favourably with that of our previous trial with cyclophosphamide and cisplatin, and also with those reported by other investigators [8, 11–16], despite the advanced stage of disease in patients we treated. Our ability to assure that this modification is indeed superior to the regimen used previously is limited, however, by the number of patients we treated.

The overall rate of long-term tumour-free survival of the patients treated in this study was 98%, with a median follow-up period of 39 months. The 2 patients who replased and were treated with cisplatin-based salvage therapy were free of disease after 32 and 42 months. This high rate of overall survival will be difficult to improve upon.

These results mirror those acheived in our other patients with advanced pure seminoma who have been treated under this strategy [8]. Although recent reports document that carboplatin is inferior to cisplatin in non-seminomatous germ cell tumours [11], carboplatin did not appear to adversely affect the outcome of patients we treated. This could be attributed to either the unique sensitivity of seminoma to platinum analogues or the strategy in which we used the drugs.

In contrast to other chemotherapy regimens reported [11–16], this combination caused no deaths in this series. The most severe complications of the carboplatin and ifosfamide combination were haematological effects. Some patients required frequent transfusions (Table 6). Neutropenic fever requiring hospitalisation was seen in only 10% of the patients. Infectious complications were rare, perhaps because there was no mucositis. There were no significant acute non-haematological toxic effects, and no long-term complications have yet been observed. This is in contrast to the moderate toxic effects suffered by patients treated with our initial regimen that incorporated the sequential delivery of cisplatin [8]. Total avoidance of the neurotoxic, ototoxic, and nephrotoxic effects that accompany cisplatin is a major advantage of the combinations of ifosfamide and carboplatin. Moreover, the frequency of non-haematological toxic effects was lower than that reported with other regimens [11–16].

Bleomycin-induced pulmonary toxic effects are reported at a higher rate in patients with seminoma than in those with non-seminomatous tumours. The difference in frequency of the occasionally fatal bleomycin effects may be a function of the older age of the patients with seminoma compared with those with non-seminomatous tumours. We believe the data we have reported here confirm the published suggestion that bleomycin is not required for therapy of seminoma [16]. In non-seminomatous tumours, bleomycin appears to be essential even in the patients with a favourable prognosis [17,18].

The contribution of each of the therapy components to the result we achieved cannot be determined. Two factors that may have contributed to the results were the selection of patients for consolidation and the selection of patients for entry into the trial. The selection of patients for consolidation was based on the

radiographic appearance of the residual mass following chemotherapy. Radiographic re-evaluation was performed after completion of every two courses of carboplatin and ifosfamide. When patients achieved maximum improvement, complete remission to chemotherapy or response to chemotherapy requiring consolidation, an additional requirement of two courses were administered. The residual mass frequenlty appeared as a poorly defined desmoplatic response (<3 cm) [8, 10]. Because patients in our earlier study, who had this characteristic response to chemotherapy, have not experienced relapse, we have since considered this response a complete remission requiring no further therapy [8]. The data of this trial confirmed the validity of that conclusion. Patients with a residual discrete mass (≥3 cm), in contrast were considered at risk of relapse [8, 10]. Such patients had fine-needle aspiration biopsy of the residual mass, followed by radiation therapy to the involved field. No biopsy revealed viable disease, indicating either that the majority have no remaining disease or that fine-needle aspiration has limited ability to detect residual viable cancer in seminoma patients following chemotherapy. In our study, the 6 patients who had a residual mass ≥3 cm in maximum transverse diameter after chemotherapy were found to have fibrosis and received immediate definitive radiation therapy. Although we realise regression continues after the completion of chemotherapy, this is a delayed event and, as per our study design, by obtaining radiographic evaluation after every two courses, we were able to determine a stable maximum improvement and thus complete chemotherapy without recognising further regression during that short time frame. The minority of patients (14%) received radiotherapy for consolidation. The dose of radiation therapy was a median of 30 Gy ranging from 25 to 36 Gy. The 6 patients remained free of disease.

Patients selected for consolidation therapy at Memorial Sloan-Kettering Cancer Center were similar, but the method of consolidation differed. The Memorial Sloan-Kettering used surgical excision with postoperative radiation therapy if viable seminoma was encountered, while we use primary radiation therapy to the involved field. We planned resection only for those patients with clinical features that led us to suspect the existence of non-seminomatous tumour. 2 patients in this clinical trial did undergo surgical exploration to exclude the possibility of histological transformation. Neither patient had viable carcinoma or teratomatous elements.

The combination of ifosfamide and carboplatin is probably inferior to existing regimens for the treatment of patients with non-seminomatous germ cell tumours. This specificity of treatment by histological type requires that precautions be taken to assure the correct histological classification of term cell cancers. Of the patients we treated, 69% had their tumour classified by histopathological study of the primary testicular cancer. An additional 16% were diagnosed by a biopsy of the metastatic site, and 15% were diagnosed by fine-needle aspiration. The study protocol required that all patients have two measurements of serum levels of AFP assayed 1 week apart and that both levels be within normal range. In none of the 42 patients we treated, did the tumour convert to a mixed histological type. Because of our ability to correctly classify the germ cell cancer, we believe review of the tumour specimen by an experienced pathologist and normal serum AFP concentrations together give a safe distinction between seminomas and non-seminomatous tumours for treatment purposes.

The strict pathological entry criteria did not adversely affect our ability to accrue representative patients with truly advanced seminoma. The clinical criteria excluded all patients but those with a retroperitoneal mass of over 10 cm in maximum transverse diameter, metastatic sites above the diaphragm, primary extragonadal origin, or radiation therapy failures (Table 3). Our patients were characteristic of those with advanced seminoma. A total of 13 patients (31%) presented with extragonadal tumours; nine of those were mediastinal, two a retropertioneal mass over 10 cm, and two pineal. The 29 patients (69%) whose tumours were of testicular origin included 19 retroperitoneal masses over 10 cm and 10 radiation therapy failures (seven with visceral metastases). The advanced stage of the disease in these patients was further reflected by their local complications (Table 4), by the performance status of some of the patients with neglected cancers, and by the frequency of elevation of both the β-HCG and LDH levels (Table 3).

Some investigators have reported an adverse treatment outcome in patients whose seminomas are of extragonadal origin, express serum tumour markers, who have a poor initial performance status, or who have already been treated by radiation therapy. Because of the high overall complete remission rates in this and other reports, we conclude that no single clinical feature of seminoma predicts an adverse outcome, and that patients with seminoma should be considered to be a favourable prognosis.

A total of 78 patients with seminoma have now been treated at M.D. Anderson with the combination of an alkylating agent and a cisplatin analogue and selective consolidation therapy (cyclophosphamide and cisplatin 36 patients, ifosfamide and carboplatin 42 patients), and 91% of these patients remain free of disease. There were no late relapses or second primary malignancies. These results support the concept of seminoma as a unique clinical entity and justify treating seminomas differently from non-seminomatous tumours. They also indicate that seminoma has a good prognosis in the era of cisplatin-based therapy. In future studies should confirm these findings, the therapeutic strategy we employed should become the treatment of choice for advanced seminoma.

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