7. Finkelstein DM, Cassileth BR, Bonomi PD, *et al.* A pilot study of the Functional Living Index—Cancer (FLIC) Scale for the assessment of quality of life for metastatic lung cancer patients. *Am J Clin Oncol* 1988, **11**, 630–633.
8. Fosså SD, Aaronson NK, Newling D, *et al.* Quality of life and treatment of hormone resistant metastatic prostatic cancer. *Eur J Cancer* 1990, **26**, 1133–1136.
9. van Holten-Verzantvoort ATM, Zwinderman AH, Aaronson NK, *et al.* The effect of supportive pamidronate treatment on aspects of quality of life of patients with advanced breast cancer. *Eur J Cancer* 1991, **27**, 544–549.
10. Hürny C, Bernhard J, Gelber RD, *et al.* Quality of life measures for patients receiving adjuvant therapy for breast cancer: An international trial. *Eur J Cancer* 1992, **28**, 118–124.
11. McMillen Moinpour C, Feigl P, Metch B, *et al.* Quality of life end points in cancer clinical trials: review and recommendations. *J Natl Cancer Inst* 1989, **81**, 485–495.
12. Aaronson NK. Methodologic issues in assessing the quality of life of cancer patients. *Cancer* 1991, **67**, 844–850.
13. Schipper H, Clinch J, Powell V. Definitions and conceptual issues. In: Spilker B, ed. *Quality of Life Assessments in Clinical Trials*. New York, Raven Press, 1990.
14. Yancik R, Edwards BK, Yates JW. Assessing the quality of life of cancer patients: practical issues in study implementation. *J Psychosoc Oncol* 1989, 7, 59–74.
15. Zwinderman AH. The measurement of change of quality of life in clinical trials. *Stat Med* 1990, **9**, 931–942.

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Papers

The Activity of Single-agent Carboplatin in Advanced Seminoma

A. Horwich, D.P. Dearnaley, R. A'Hern, M. Mason, G. Thomas, G. Jay and J. Nicholls

Between 1982 and 1990, 70 patients with advanced metastatic seminoma were treated with 4–6 courses of single-agent carboplatin (SAC) administered at 400 mg/m^2 every 3–4 weeks. Treatment was of low toxicity and no patients suffered neurotoxicity, ototoxicity or significant renal damage. There was only one episode of neutropenic sepsis and no thrombocytopenic bleeding. The median follow-up of surviving patients was 3 years. 16 patients have relapsed and 4 of these 16 have died, thus the actuarial 3-year relapse-free survival was 77% (95% CI 65–86%), cause-specific survival was 94% (95% CI 82–99%) and overall survival was 91% (95% CI 80–96%). The risk of relapse was reduced by post-chemotherapy irradiation (PCRT) to involved nodes, occurring in 1/20 patients treated with PCRT compared with 11/31 who could have been treated but were not ($P = 0.04$). Of the 16 patients who relapsed, 12(75%) have been salvaged with combination chemotherapy and remain free from further relapse with a median follow-up of 18 months. Though this level of survival is equivalent to that obtained with initial cisplatin-based combination chemotherapy, the recurrence rate indicates that SAC remains an investigative treatment, except for unfit patients.
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INTRODUCTION

METASTATIC SEMINOMA is exquisitely sensitive to platinum-based chemotherapy regimens [1, 2]. There is little controversy over the use of chemotherapy for patients with stage III or IV seminoma or for stage II seminoma with abdominal node mass greater than 10 cm in diameter. However, for smaller volume stage II disease, the results of a relatively short course of retroperitoneal radiotherapy are very good [3]. A retrospective study at the Royal Marsden Hospital (RMH) demonstrated an increased recurrence rate after radiotherapy for retroperitoneal node masses more than 5 cm in diameter [4] and we have thus used initial combination chemotherapy in the management of patients with RMH stage IIC, III and IV tumours as well as for primary mediastinal seminomas (Table 1).

Our early experience of 34 patients with advanced metastatic seminoma treated with single-agent carboplatin suggested that this formed an effective and non-toxic treatment [5]. We have now extended this experience to a total of 70 patients treated between 1982 and 1990, and have analysed the impact of post-chemotherapy irradiation.

Patients and methods

Patients referred to the Testicular Tumour Unit at the Royal Marsden Hospital between 1982 and 1990 with a diagnosis of

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Table 1. RMH staging and distribution of patients

II Abdominal lymphadenopathy	
A <2 cm	1
B 2–5 cm	3
C >5 cm	26
III Supradiaphragmatic lymphadenopathy	26
IV Extranodal metastases	10
Med Mediastinal primary	4
Total	70

seminoma were assessed by review of histology, assay of the serum tumour markers, human chorionic gonadotropin (HCG), and alphafetoprotein (AFP) and computed tomography (CT) of thorax and abdomen. The glomerular filtration rate (GFR) was assessed in all patients by excretion of chromium-51 EDTA clearance. The RMH staging (Table 1) was used and patients with stage IIC, III or IV disease were eligible for treatment with single-agent carboplatin with the exception of patients with more than three lung metastases, liver metastases or an abnormal serum alphafetoprotein level (more than 15 U/l). 4 patients had primary mediastinal seminomas and the stage distribution of the remaining 66 patients at the time of protocol entry is shown in Table 1. It can be seen that 1 patient had stage IIA disease, 29 stage IIC, 26 stage III and 10 stage IV. Immediately prior to chemotherapy, 4 patients had serum HCG of more than 100 U/l (101–920 U/l) and a further 7 patients had levels between 50 and 100 U/l. 36 patients had a raised serum HCG of more than 5 U/l, and 25 of more than 10 U/l.

The mean age of the 70 patients was 36.8 years, range 21–65 years. Pre-existing general medical illness included Down's syndrome with pulmonary hypertension (1 patient), alcoholism (1 patient), severe chronic respiratory disease (1 patient) and bulbar palsy (1 patient).

Carboplatin, 400 mg/m^2, was infused intravenously over 1 h in 500 ml of 5% dextrose cycled every 21–28 days. The administered dose was corrected for major abnormalities of renal clearance (GFR) to allow for different rates of renal excretion [6]. The dose was escalated to 440 mg/m^2 for patients with a glomerular filtration rate between 120 and 140 mls/min and to 460 mg/m^2 for GFR greater than 140 ml/min. The dose was reduced to 350 mg/m^2 for patients with GFR between 60 and 80 mls/min, to 300 mg/m^2 for GFR between 40 and 60 ml/min, to 200 mg/m^2 for GRF between 25 and 40 ml/min. 20 patients received six courses of carboplatin, 2 received five courses, 46 received four courses, 1 patient with a large mediastinal mass died after the first course of respiratory obstruction. There were no strict criteria for continuing to more than four courses of chemotherapy, however, this was more common in stage IV patients and in patients with a large mass.

Radiotherapy was not used routinely after chemotherapy, even in patients with residual abnormalities seen on CT scan. The initial involved site was treated in 20 patients following carboplatin, 3 mediastinal primaries, 10 stage II patients and 7 stage III. Usually, the originally involved nodal group was treated to the residual volume using parallel opposed fields from a 6 MeV linear accelerator, to a dose of 30–35 Gy in 15–20 fractions over 3–4 weeks.

Patients relapsing after carboplatin were treated with intensive bleomycin, vincristine and cisplatin (BOP) induction chemotherapy [7]. Following 4 weeks of this intensive induction and a 2-week gap, three courses of bleomycin, etoposide and cisplatin (BEP) [8, 9] chemotherapy with half the standard bleomycin dose were administered. The sites of relapse were treated with radiotherapy whenever feasible. 1 patient relapsing after carboplatin was treated with BEP chemotherapy alone, unsuccessfully.

Survival and freedom from progression were assessed from the first day of carboplatin chemotherapy. For the purpose of analysis, 2 patients who never became disease-free were considered to have relapsed on day 1. Survival plots included all causes of death, but analyses of failure-free survival and cause-specific survival censored patients dying from coincidental disease. Differences between relapse-free survival curves were analysed by log rank testing.

RESULTS

70 patients were treated with single-agent carboplatin between March 1982 and January 1990. All patients had completed treatment at least 8 months before analysis. 2 patients died of intercurrent disease while apparently in remission. 1 of these had Down's syndrome and developed complications of a cardiac septal defect. The other had a history of alcoholism and developed a second primary tumour of the tonsil. 1 patient with massive mediastinal recurrence after radiotherapy for stage II seminoma collapsed with bronchial obstruction 12 h following his initial dose of carboplatin and died 2 weeks later and this was counted as a cause-related death.

Deaths from progressive seminoma included 1 patient presenting with a 2-year history of massive neglected primary testicular seminoma extending along the cord into the retroperitoneal area. He was treated with carboplatin for stage IIC disease but progressed with enlarging lymphadenopathy and ascites after the third course. His disease was refractory to BEP salvage. 2 patients treated for stage II seminoma relapsed with extensive AFP-positive malignant disease which was refractory to further treatment. 1 of these relapsed 3 months after chemotherapy, in pelvic nodes, and with a mass in the loin; the other relapsed at 4 months with mediastinal and pelvic node disease. These patients both died. The fourth patient to die of seminoma had previously had radiotherapy for stage II disease, and was treated with carboplatin for mediastinal and lung relapse. His partial response

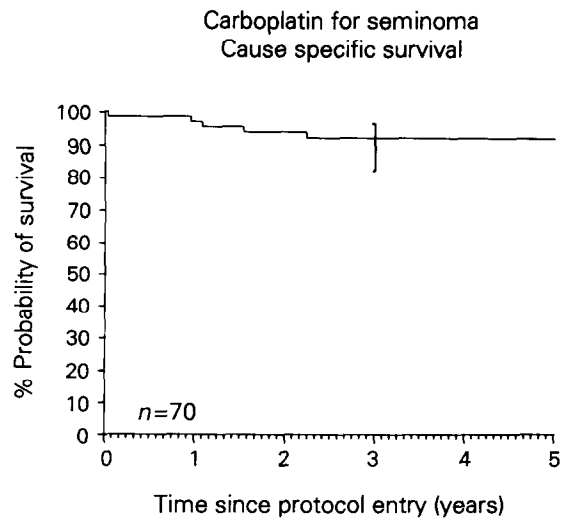

Fig. 1. Cause-specific survival of 70 patients treated with carboplatin for seminoma. The bar represents the 95% confidence interval.

Table 2. Carboplatin for seminoma (RMH 1982–90)

Patients		70
Follow-up	range	8–101 months
	median	36 months
Early death		1
Relapse		16
Salvage from relapse		12
Follow-up after salvage	range	8–90 months
	median	18 months
Intercurrent death		2
3-year relapse-free		74%
3-year cause-specific survival		95%

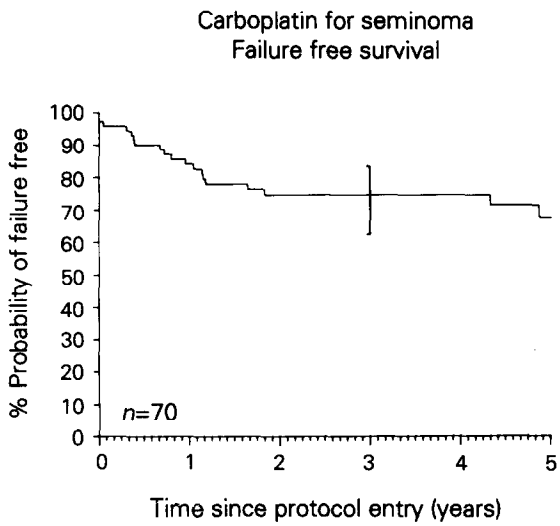

Fig. 2. Failure-free survival after carboplatin for seminoma. The bar represents the 95% confidence interval.

lasted only 1 month, and despite a 9-month complete remission after combination chemotherapy, recurrence occurred at the same sites. The actuarial cause-specific survival of the series of 70 patients at 3 years after the start of carboplatin was 94% (95% CI 82–99%), and overall 3-year survival was 91% (95% CI 80–96%) (Fig. 1).

As shown in Table 2, 16 patients have relapsed. The very predominant relapse pattern was in the first 2 years after treatment (Fig. 2), though the latest relapse was at 4.5 years. Of the 16 patients who relapsed, 15 were treated with intensive BOP/BEP combination chemotherapy and 12 (75%) of the 16 have remained free from further relapse for 8 to 90 months (median 18 months) after treatment. Levels of the following factors were examined by log rank analysis of progression-free survival curves; serum HCG concentration (Table 3), prior

Table 3. Significance of serum HCG

Serum HCG (U/l)	Patients	Relapse
<2	14	3(21%)
2–10	29	3(28%)
11–50	14	1(7%)
>50	11	3(27%)

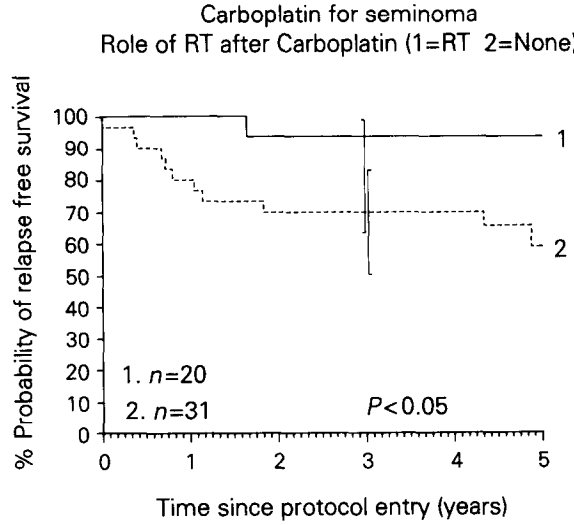

Fig. 3. Failure-free survival comparing 20 patients irradiated after carboplatin [1] with 31 patients not irradiated [2] ($P < 0.01$). The analysis was confined to patients with stage II or III seminoma who had completed four courses of carboplatin and could have been treated with an extended radiotherapy field. The bar represents the 95% confidence interval.

radiotherapy, age, stage, cycle time and number of courses of carboplatin; no significance differences were detected. Relapse after carboplatin occurred in 1/4 mediastinal primaries, 8/30 stage II patients, 4/26 stage III and 3/10 stage IV (non-significant). Other prognostic variables analysed to attempt to define risk of relapse included carboplatin dose expressed as serum concentration × time, partial vs. complete response, and the benefit of adjuvant post-chemotherapy radiation (PCRT), which was examined only in those considered eligible for radiotherapy, namely patients with nodal disease, whose lymphadenopathy at the time of carboplatin was confined to one side of the diaphragm and had not been irradiated previously. PCRT was the only one of these factors to influence recurrence. It was employed in 3 patients with mediastinal primary, and 17 with stage II or III seminoma. By 2 years after the start of carboplatin, relapse had occurred in 11 of 31 patients treated with chemotherapy alone, compared with only 1 of 20 who also had adjuvant radiotherapy ($P = 0.04$, log rank test) as shown in Fig. 3. 22 patients had previously had radiotherapy for small volume stage II seminoma, and were treated with carboplatin at the time of relapse. Their relapse and survival rate were not different from patients who had not had prior radiotherapy (Fig. 4).

Response to carboplatin chemotherapy was assessed radiologically by CT scanning within 3 weeks of completing chemotherapy. There was complete radiological remission in 13 patients (of whom 4 relapsed) and the remainder had residual masses monitored by further CT. An assessment of carboplatin exposure per course of treatment was calculated as the serum concentration . Time curve (AUC), derived from the administered dose and the glomerular filtration rate according to dose = AUC (GFR + 25) mg [6]. This was 5.3 mg/ml . min in patients who relapsed and 5.9 mg/ml . min in those who did not (non-significant).

Toxicity of treatment

The most common side-effects of carboplatin treatment were nausea and vomiting, which typically occurred 6–18 h following administration of the drug. Patients were routinely pretreated

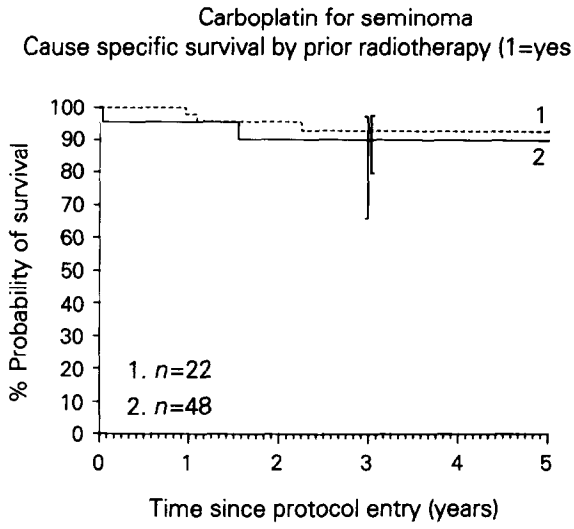

Fig. 4. Cause-specific survival of 22 patients who had previously had radiotherapy [1], compared with 48 patients who had not [2] (no significant difference). The bar represents the 95% confidence interval.

with anti-emetics (dexamethasone and either prochloprazine or metaclopromide). No patients experienced symptomatic peripheral neuropathy, ototoxicity, parasthesiae or muscle cramps.

31 patients had renal function re-assessed by a repeat assay of glomerular filtration rate using chromium-51-labelled EDTA clearance. 7 patients had a fall in GFR of more than 10% and these patients have been analysed in detail and reported separately [10]. Haematological toxicity is shown in Table 4. Only 1 patient suffered neutropenic sepsis and no patients had thrombocytopenic bleeding.

DISCUSSION

This report brings up to date our experience of single-agent carboplatin in advanced seminoma and includes the 34 patients previously reported [5]. Experience in 70 patients has confirmed the exquisite sensitivity of seminoma to single-agent carboplatin, however, although the treatment is of low toxicity, approximately 1 in 4 patients is destined to relapse after carboplatin and will require combination chemotherapy. This rose to 1 in 3 in patients not irradiated after carboplatin, and fell to 1 in 20 if radiotherapy was used ($p = 0.04$). The overall cure rate with this approach is equivalent to using combination chemotherapy at the outset, however, carboplatin alone is clearly only safe for a patient who can be closely monitored following treatment. This study has not revealed clear prognostic factors and, in particular, would not support the suggestion that bulky residual masses indicate an adverse prognosis [11]. The dose schedule allows an analysis of dose–response based on calculated serum concentration × time. Within a limited range, we cannot determine any influence of carboplatin dose on control.

Preliminary confirmation of the activity of single agent carboplatin in seminoma has come from Schmoll *et al.* [12] and from Dieckmann *et al.* [13] who have reported progression-free survival in more than 75% of patients, 28/35 and 6/6, respectively. The recurrence rate discerned in our study of single-agent carboplatin appears to be higher than our previous experience with cisplatin-based combination chemotherapy [2]. The difference is not significant and does not translate to any difference in survival, but nevertheless, the use of single-agent carboplatin in seminoma should be regarded at present as a research investigation, except in patients not fit enough for standard cisplatin-based therapy. The Medical Research Council Testicular Tumour Working Party is currently pursuing a prospective randomised trial in stage IIC, III and IV metastatic testicular seminoma comparing single-agent carboplatin with the combination of etoposide + cisplatin, and the rarity of these stages of seminoma makes it important for specialised centres to support this trial.

Table 4. Haematological toxicity: nadir blood counts

Course	1	2	3	4
Total evaluable patients	60	68	66	67
Patients with platelets $<100 \times 10^9/l$	4	7	13	11
$<50 \times 10^9/l$	1	3	3	5
Patients with WBC $<1.5 \times 10^9/l$	1	0	1	0
$<0.5 \times 10^9/l$	0	0	0	0

1. Einhorn LH, Williams SD. Chemotherapy of disseminated testicular cancer: a random prospective study. *Cancer* 1980, **46**, 1339–1344.
2. Peckham MJ, Horwich A, Hendry WF. Advanced seminoma: treatment with Cis-platinum-based combination chemotherapy or carboplatin (JM8). *Br J Cancer* 1985, **52**, 7–13.
3. Thomas G. Management of metastatic seminoma: role of radiotherapy. In: Horwich A, ed. *Testicular Cancer—Clinical Investigation and Management*. London, Chapman and Hall Medical, 1991, 211–231.
4. Gregory C, Peckham MJ. Results of radiotherapy for stage II testicular seminoma. *Radiotherapy and Oncology* 1986, **6**, 285–292.
5. Horwich A, Dearnaley DP, Duchesne GM, Williams M, Brada M, Peckham MJ. Simple non-toxic treatment of advanced metastatic seminoma with carboplatin. *J Clin Oncol* 1989, **7**, 1150–1156.
6. Calvert AH, Newell DR, Gumbrell LA, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989, **7**, 1748–1756.
7. Horwich A, Brada M, Nicholls J, *et al.* Intensive induction chemotherapy for poor risk non-seminomatous germ cell tumours. *Eur J Cancer Clin Oncol* 1989, **25**, 177–184.
8. Peckham MJ, Barrett A, Liew K, *et al.* The treatment of metastatic germ-cell testicular tumours with Bleomycin, Etoposide and Cisplatinum (BEP). *Br J Cancer* 1983, **47**, 613–619.
9. Dearnaley DP, Horwich A, A'Hern R, *et al.* Combination chemotherapy with bleomycin, etoposide and cisplatin (BEP) for metastatic testicular teratoma: long-term follow-up. *Eur J Cancer* 1991, **27**, 684–691.
10. Mason MD, Nicholls J, Horwich A. The effect of carboplatin on renal function in patients with metastatic germ cell tumours. *Br J Cancer* 1991, **63**, 630–633.
11. Motzer RJ, Bosl GJ, Geller NL, *et al.* Advanced seminoma: the role of chemotherapy and adjunctive surgery. *Annals of Internal Med* 1988, **108**, 513–518.
12. Schmoll H-J, Bokemeyer C, Harstrick A, *et al.* Single agent carboplatinum (CBDCA) for advanced seminoma: a phase II study. *Proc ASCO* 1991, **10**, 181.
13. Dieckmann K, Bornhoeft G, Huland H. Ambulante carboplatin-monotherapie beim fortgeschrittenen seminom. *Urologe A* 1990, **29**, 281–285.

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