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Original Paper

POMB/ACE Chemotherapy for Mediastinal Germ Cell Tumours

M. Bower,[1] C. Brock,[1] L. Holden,[1] A. Nelstrop,[2] A.R. Makey,[3] G.J.S. Rustin[2] and E.S. Newlands[1]

[1]Medical Oncology Unit, Charing Cross Hospital, Fulham Palace Road, London W6 8RF; [2]Mount Vernon Centre for Cancer, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN; and [3]Department of Thoracic Surgery, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, U.K.

Mediastinal germ cell tumours (MGCT) are rare and most published series reflect the experiences of individual institutions over many years. Since 1979, we have treated 16 men (12 non-seminomatous germ cell tumours and 4 seminomas) with newly diagnosed primary MGCT with POMB/ACE chemotherapy and elective surgical resection of residual masses. This approach yielded complete remissions in 15/16 (94%) patients. The median follow-up was 6.0 years and no relapses occurred more than 2 years after treatment. The 5 year overall survival in the non-seminomatous germ cell tumours (NSGCT) is 73% (95% confidence interval 43–90%). One patient with NSGCT developed drug-resistant disease and died without achieving remission and 2 patients died of relapsed disease. In addition, 4 patients with bulky and/or metastatic seminoma were treated with POMB/ACE. One died of treatment-related neutropenic sepsis in complete remission and one died of relapsed disease. Finally, 4 patients (2 NSGCT and 2 seminomas) referred at relapse were treated with POMB/ACE and one was successfully salvaged. The combination of POMB/ACE chemotherapy and surgery is effective management for MGCT producing high long-term survival rates. © **1997 Elsevier Science Ltd.**

Key words: mediastinal germ cell tumour, chemotherapy, teratoma, germinoma

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INTRODUCTION

APPROXIMATELY 2–6% of all malignant germ cell tumours (GCT) are thought to have extragonadal origins and the anterior mediastinum is the most common site [1]. In adults, over 90% of malignant primary mediastinal germ cell tumours (MGCT) of all histologies occur in men, although in children these tumours are equally distributed between the genders [2, 3]. Patients usually present in the second to fourth decade of life with chest pain, dyspnoea, cough (with or without haemopytsis) and constitutional symptoms such as weight loss and fevers.

The prognosis for these tumours has been reported to be inferior to that for metastatic germ cell tumours of gonadal origin [4–7]. However, with the advent of platinum-based combination chemotherapy followed by elective thoracotomy to remove residual tissue, the outcome has improved [8].

Published results of chemotherapy of MGCT were compiled in a recent review of the literature and reported long-term disease-free status rates of 28/37 (76%) for mediastinal seminomas and 90/204 (44%) for non-seminomatous MGCTs [9]. On account of the rarity of these tumours, most publications reflect the experiences of single institutions over several years and the patients have usually received a variety of different chemotherapy schedules. Furthermore, the current prognosis for MGCT is difficult to assess since most series include patients treated a long time ago. Here, we report our experience of treating patients with MGCT with POMB/ACE chemotherapy and elective surgical resection of residual masses.

Correspondence to M. Bower.
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PATIENTS AND METHODS

Since 1979 the standard first-line chemotherapy regime for germ cell tumours at our institution has been POMB/ACE [10]. 16 patients with MGCTs (12 NSGCT and 4 seminomas) have been treated with this chemotherapy schedule for primary disease as have a further 4 patients referred at relapse following initial chemotherapy or radiotherapy. The criteria for diagnosis of MGCT included a mass in the anterior mediastinum, histological or serological evidence of germ cell tumours and normal testes on initial and subsequent examinations. The median follow-up for the primary MGCT patients is 6.0 years (range 0.7–15.1).

The patients with primary MGCTs were all male and their median age was 29 years (range 14–63). A biopsy of the tumour prior to treatment was obtained from all but one patient (patient 1) who presented with severe respiratory distress, a 10 cm anterior mediastinal mass with bilateral pleural effusions and a serum α-fetoprotein (APF) of 35370 IU/l. Thoracotomy was performed following six cycles of POMB/ACE chemotherapy which revealed residual active malignant teratoma undifferentiated (MTU).

The clinicopathological features of the patients are listed in Table 1. Both serum AFP and β-human chorionic gonadotrophin (hCG) were measured at presentation for all patients and in only two cases was neither marker elevated at presentation (Tables 2 and 3).

POMB/ACE chemotherapy consists of cisplatinum, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide. Each course comprises 3–4 days chemotherapy administered at fortnightly intervals. The first two courses comprise POMB and thereafter POMB and ACE courses alternately [10]. 8 patients who presented with marked dyspnoea or bulky mediastinal disease were induced with low-dose platinum (20 mg/m^2) and etoposide (100 mg/m^2) daily for 2 or 3 days and POMB/ACE commenced one week later.

Statistical methods

Survival was calculated from the first day of treatment until death or the date of last follow-up. Overall survival duration curves were plotted according to the method of Kaplan and Meier [11].

Table 1. Clinicopathological details of 16 patients with newly diagnosed MGCT

	All	NSGCT	Seminoma
Clinical presentations			
Dyspnoea	11	10	1
Pain	14	12	2
Chest pain	14	12	2
Back pain	2	2	0
Gynaecomastia	5	4	1
Superior vena cava obstruction	4	4	0
Haemoptysis	1	1	0
Disease extent at presentation			
Confined to mediastinum	3	1	2
Mediastinum and effusion only	4	3	1
Parenchymal metastases	9	8	1
Size of mediastinal mass			
0–4 cm (maximal diameter)	2	2	0
5–9 cm	2	1	1
10–14 cm	8	6	2
15–19 cm	2	1	1
≥20 cm	2	2	0

Table 2. Serum tumour markers at presentation

Histology	Raised AFP only	Raised hCG only	Both raised	Neither raised
Teratoma	5	1	6	0
Seminoma	0	2	0	2
Total	5	3	6	2

AFP, α-fetoprotein; hCG, β-human chorionic gonadotrophin.

RESULTS

The overall 5 year survival for the 16 newly diagnosed patients was 71% (95% confidence interval 45–88%) and no deaths or relapses occurred later than 2 years after the start of chemotherapy (Figure 1). All 16 primary MGCTs demonstrated initial responsiveness to POMB/ACE chemotherapy as evidenced by declining tumour markers and decreasing tumour masses, with 15/16 CRs (94%).

Non-seminomatous germ cell tumours

The overall 5 year survival for the 12 patients with non-seminomatous MGCTs is 73% (95% confidence interval 43–90%). The median survival for these patients has not yet been reached. Elective early thoracotomy was undertaken following 6–9 courses of POMB/ACE chemotherapy for all 12 patients with mediastinal NSGCT. The early surgical intervention makes evaluation of response rates by conventional criteria difficult, but active tumour was only present in 2/12 resection specimens; one of these was the patient (patient 1) who started treatment without a biopsy and in whom the surgery was performed relatively early to confirm the diagnosis histologically—a further five courses of POMB/ACE were administered postoperatively. The histology in the remaining 10 cases was necrotic tumour ($n = 5$) or differentiated teratoma ($n = 5$) (Table 3).

Only one patient (patient 3) demonstrated evidence of active residual disease at the completion of POMB/ACE. He had undergone debulking of a 13 × 10 × 7 cm mediastinal MTU tumour at diagnosis followed by nine courses of POMB/ACE. At second thoracotomy following chemotherapy, there remained active tumour that could not be completely resected and despite salvage chemotherapy, remission was never achieved and he died of progressive disease.

A further 2 men with mediastinal NSGCT died. One patient developed isolated cerebral metastasis following chemotherapy and thoracotomy (patient 2) and died of progressive disease despite craniotomy and salvage chemotherapy. The other patient (patient 5) developed acute myeloid leukaemia and evidence of recurrent MGCT 6 months after achieving complete remission and died following salvage chemotherapy. Cytogenetic analysis of the malignant clone of blast cells revealed a complex karyotype with abnormalities of chromosome 5 which are associated with secondary leukaemias. The clones included neither the isochromosome i(12p) nor rearrangements of chromosome 11q23. He had received a total dose of 900 mg/m^2 of etoposide.

Table 3. Details of individual patients

Patient	Age (years)	Histology	AFP (IU/l)	hCG (IU/l)	POMB/ACE courses	Histology at surgery	Outcome: chemotherapy and surgery	Follow-up (months)
1	20	MTU	35370	<2	11	Active tumour	CR	160
2	20	MTU	23230	4	7	Necrotic tumour	Relapse (CNS) (after CR)	13 DoD
3	27	MTU	800	<2	9	Active tumour	Progressive disease	13 DoD
4	43	MTU	41000	35	10	Differentiated teratoma	CR	181
5	29	MTI	1095	17	6	Differentiated teratoma	Relapse (& AML) (after CR)	19 DoD
6	29	MTI	3989	46	10	Differentiated teratoma	CR	159
7	44	MTU	9876	2	9	Necrotic tumour	CR	107
8	14	MTU	4613	2450	10	Necrotic tumour	CR	88
9	24	MTT	<2	999776	10	Necrotic tumour	CR	173
10	28	MTU	44610	<2	7	Differentiated teratoma	CR	97
11	25	MTU	1545	26	7	Necrotic tumour	CR	37
12	33	MTU	54	9465	5	Differentiated teratoma	CR	7
13	39	Seminoma	<2	<2	6	Necrotic tumour	CR	25
14	43	Seminoma	<2	9	6	No surgery	Relapse (after CR)	8 DoD
15	24	Seminoma	3	115	7	No surgery	CR	72
16	63	Seminoma	<2	<2	3	No surgery	Toxic death (in CR)	0

AML, acute myeloid leukaemia; AFP, α-fetoprotein, at presentation; CR, complete remission; hCG, human chorionic gonadotrophin, at presentation; DoD, dead of disease; MTU, malignant teratoma undifferentiated; MTT, malignant teratoma trophoblastic; MTI, malignant teratoma intermediate.

Seminoma

The planned approach for bulky (>10 cm diameter) or metastatic mediastinal seminoma was POMB/ACE chemotherapy followed by surgical resection of residual masses >3 cm and elective mediastinal radiotherapy. However, one patient (patient 13) with seminomatous MGCT underwent thoracotomy following four courses of POMB/ACE as he appeared to be developing a necrotic mediastinal abscess. This patient did not receive postoperative irradiation as right ventricular hypertrophy was noted at surgery and two additional cycles of chemotherapy were substituted. A second patient (patient 14) with mediastinal seminoma relapsed within 2 months of completing six courses of POMB/ACE before the planned radiotherapy. A third patient (patient 15) with mediastinal seminoma received radiotherapy following completion of chemotherapy without surgery as there were no residual abnormalities on the thoracic CT scan. The final patient with mediastinal seminoma (patient 16) died of neutropenic sepsis whilst on treatment.

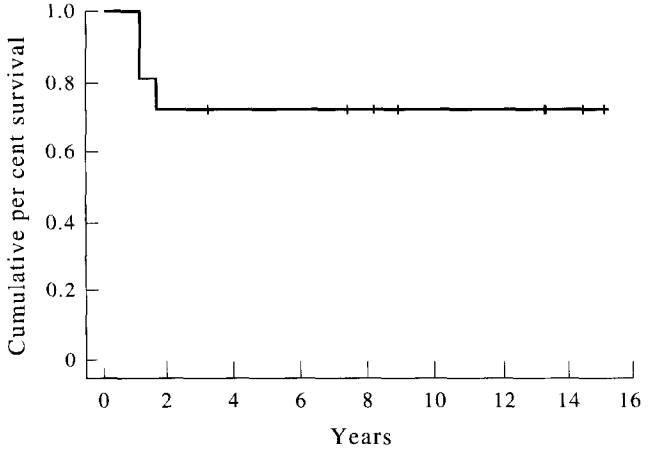

Figure 1. Overall survival of primary mediastinal NSGCT patients treated with POMB/ACE chemotherapy.

Relapsed MGCT

In addition, 4 patients who were referred at relapse were treated with POMB/ACE. One 18-year-old man initially received MOPP (mustine, vincristine, procarbazine, prednisolone) combination chemotherapy for presumed mediastinal Hodgkin's disease. A biopsy on completion of the chemotherapy revealed adenocarcinoma and he received radiotherapy. He relapsed 2 months later with an elevated AFP (22000 IU/l) and was referred to Charing Cross Hospital. He was treated with four cycles of POMB/ACE chemotherapy but the disease progressed. This was followed by incomplete resection that revealed active MTU. However, despite further chemotherapy he died of disease.

A second patient was referred at relapse following surgical resection and postoperative PVB (platinum, vinblastine and bleomycin) chemotherapy for mediastinal malignant teratoma (MTU). He relapsed 6 months after completing chemotherapy and received 10 cycles of POMB/ACE with a good serological response. This was followed by debulking thoracotomy that demonstrated active teratoma. Postoperative chemotherapy was administered, but the disease progressed and the patient died of active tumour.

The third patient was a 20-year-old man with a mediastinal seminoma that was completely excised and treated with postoperative radiotherapy. He relapsed 1 month later with involvement of the right acetabulum and received seven cycles of POMB/ACE combination chemotherapy for metastatic mediastinal seminoma and remains in complete remission 5 years later. The fourth patient was a 19-year-old man with mediastinal seminoma that had responded poorly to initial radiotherapy and was commenced on POMB/ACE che-

motherapy. There was an initial response to POMB/ACE, but drug resistance developed and he died of disease.

Toxicity

Alopecia and nausea were universally experienced, although the severity of the latter was reduced dramatically following the introduction of 5-HT_3 antagonists in the 1990s. Dosage reductions were instituted for 4/14 (29%) patients due to WHO grade 3/4 infection or grade 1/2 nephrotoxicity [12]. All patients experienced grade 3/4 leucopenia and one patient developed grade 4 thrombocytopenia. The use of colony stimulating factors has been available since 1990 to maintain dose intensity in leucopenic patients on POMB/ACE chemotherapy. There was a single toxic death due to neutropenic sepsis in a 63-year-old with mediastinal seminoma who had achieved radiological and serological remission (patient 16).

DISCUSSION

It is widely believed that extragonadal GCT have a worse prognosis than testicular germ cell tumours. In the case of retroperitoneal GCT this may be due to advanced presentation, whilst MGCT appears to be less chemosensitive, and this is especially notable for recurrent tumours [7]. In this series, all patients with NSMGCT had bulky disease and/or high serum tumour markers, factors that have been identified as poor prognostic indicators [13]. The poor prognosis of MGCT has also been attributed to an association with haematological malignancy [14].

There exists a definite association between mediastinal NSGCT and haematological tumours including acute leukaemias, megakaryocytic disorders and malignant histiocytosis. One hypothesis to explain this association proposes that the multipotential germ cells may differentiate along haematopoietic lines in the appropriate environment. The isochromosome of 12p is a characteristic karyotypic abnormality of all forms of testicular germ cell tumours. The finding of the i(12p) marker in both the mediastinal NSGCT and associated leukaemic blasts from the same patient supports this hypothesis [14]. In addition, secondary acute myeliod leukaemias have been reported in patients treated for germ cell tumours with chemotherapy including topoisomerase II inhibitors [15]. The etoposide related leukaemias typically occur within 2 years of therapy and often demonstrate chromosomal abnormalities of chromosome band 11q23 with rearrangement of the mixed lineage leukaemia (MLL) gene [16].

In the precisplatinum era, the prognosis for mediastinal NSGCT was very poor and in 1975 Cox reported no survivors amongst 35 patients [2]. However, an analysis of the results since the introduction of platinum chemotherapy has suggested that 44% NSMGCT achieve long-term disease-free status [9]. Recently published series report that higher response rates of 50–80% and disease-free survival rates of 47–73% can be achieved using combination chemotherapy and surgery [8, 17–21]. Our experience of POMB/ACE chemotherapy followed by surgery for NSMGCT yielded a complete remission rate of 11/12 (92%, 95% confidence interval: 73–100%) and a 5 year disease-free survival of 73% (95% confidence interval 43–90%).

Elective thoracotomy is essential in the management of NSMGCT and the timing of surgery appears to be of considerable importance [7, 8, 22]. Attempts at complete resection or major debulking surgery at diagnosis will delay the start of chemotherapy and may compromise outcome. In addition, delaying surgery too long by waiting until serum markers have returned to normal values risks allowing the development of drug-resistant disease within large tumour masses. Our policy is to administer 6–9 cycles of POMB/ACE over 12–18 weeks followed by elective surgery to remove all residual masses. If there is evidence of active tumour in the resected specimens, further cycles of chemotherapy are recommended.

This series included only 4 patients with mediastinal seminomas. These tumours are radiosensitive and patients with relatively small localised tumours are frequently treated with radiation and not referred to our unit. Patients with bulky or metastatic seminomatous MGCT should be treated with chemotherapy initially. All 4 patients in this series had bulky tumours (>10 cm in diameter) and/or metastatic disease. Following completion of chemotherapy, we advocate the surgical resection of residual masses of $\geqslant$3 cm and adjuvant radiotherapy. Some groups favour additional chemotherapy if active tumour is present at thoracotomy and surveillance if only necrotic tissue is found. In contrast, for advanced retroperitoneal seminoma, observation alone for residual masses of <3 cm following chemotherapy is advocated [23, 24].

2 patients with NSMGCT received POMB/ACE chemotherapy at relapse, but neither achieved a complete remission and both died. Similarly disappointing results have been reported for other salvage chemotherapy regimens including high-dose chemotherapy with autologous progenitor cell rescue [25–27]. The poor response to salvage therapy compared to primary treatment has been noted in ovarian GCTs for POMB/ACE [28]. The chemoresistance of relapsed extragonadal and ovarian GCTs compared to testicular primary GCTs may relate to biological differences between GCTs of different origins.

The prognosis of primary MGCT in the modern era appears to have improved. However, the outcome at relapse remains dismal and thus carefully integrated multidisciplinary management of primary disease is of paramount importance.

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