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Acknowledgements—This study was supported by The Netherlands Cancer Foundation grant AUKC VU 83-7 and Bristol Myers Co.

Eur J Cancer, Vol. 27, No. 3, pp. 273–277, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Multimodality Treatment of Malignant Germ Cell Tumours of the Mediastinum

Giuseppe Giaccone

Of 15 patients with malignant germ cell tumours of the mediastinum, 9 patients had pure seminomas and 6 had non-seminomas. Resection was radical in only 4 non-seminomas, 1 of which was resected after chemotherapy; radiotherapy was delivered to all seminoma patients as sole therapy (2 patients) or as part of combined modality therapy. All patients with non-seminomatous tumours underwent chemotherapy (cisplatin-based combination). Therapy was generally well tolerated, but 1 seminoma patient died of sepsis. Chemotherapy achieved a 71% complete response rate in pure seminoma patients and a 33% complete response rate in non-seminoma patients. 53% of patients are alive and free of disease beyond 36 months from start of any treatment. Pure seminoma patients survived longer than non-seminoma patients (3 and 5 year survivals were 67% and 33%, respectively). Although cisplatin-based chemotherapy is highly effective in pure seminomas and also in non-seminomas, a better therapeutic approach is needed in non-seminomas.
Eur J Cancer, Vol. 27, No. 3, pp. 273–277, 1991.

INTRODUCTION

GERM CELL tumours of the mediastinum are rare neoplasms, histologically indistinguishable from those arising in the gonads. The mediastinum represents the third most frequent site of malignant germ cell tumours, after testes and retroperitoneum; moreover, germ cell tumours represent about 10% of all mediastinal tumours [1, 2].

A few small series have been reported and therapy for this disease is a matter of debate. Complete resection is often impossible and pure seminomatous tumours are usually treated with mediastinal irradiation [3]. Non-seminomatous tumours are often treated with chemotherapy [4, 5]. The introduction of cisplatin in combination chemotherapy for testicular tumours in the late 1970s has dramatically improved the poor prognosis

Table 1. Symptoms at diagnosis

Symptom	No. of patients
Cough and dyspnoea	10 (67%)
Chest pain	7 (47%)
Superior vena caval syndrome	7 (47%)
Fever	6 (40%)
Weight loss	5 (33%)
Asthenia	3 (20%)
Sweating	2 (13%)
Gynaecomastia	1 (7%)

of patients with non-seminomatous tumours [6]. Current chemotherapy regimens containing high doses of cisplatin (100 mg/m^2 or more) followed by cytoreductive surgery achieve complete remission in approximately 80% of patients with advanced non-seminomatous testicular cancer with about 70% rate long-term survival [7]. Unfortunately, a similar approach to the treatment of extragonadal germ cell tumours has had fewer responses and shorter survival times [8–11].

We describe our experience with 15 young patients with malignant germ cell tumours of the mediastinum treated primarily with cisplatin-containing chemotherapy in a single institution.

PATIENTS AND METHODS

From August 1980 to September 1987, 15 patients were observed with histologically confirmed, malignant germ cell tumours of the mediastinum in the absence of clinically detectable testicular or retroperitoneal masses. Pathological material was classified according to the WHO guidelines [12]. Initial histological diagnosis was modified in 4 cases: small cell lung carcinoma had been diagnosed in 1 case and thymoma in 3 other cases. 9 of the 15 patients (60%) had pure seminoma histologies; the remaining 6 patients had non-seminamatous tumours. The median age at diagnosis was 26 years (range 19–45; median 28 for seminoma and 25.5 for non-seminoma patients). Only patient 6 was female. All but patient 8 had symptoms at diagnosis (Table 1). The mean time from development of initial symptoms to diagnosis was 34 days (range 15–70).

Diagnosis was obtained by mediastinal biopsy in all patients and was done during mediastinoscopy in 5 patients, exploratory thoractomy in 8 and transthoracic needle biopsy in 2. All patients had chest X-ray and computed tomography (CT); chest tomography, radioisotopic lung scanning and bronchoscopy were done in individual cases. The tumour was easily seen on chest X-ray and CT in all patients; the largest neoplasm measured 22 cm in maximum diameter (patient 10). All neoplastic lesions were located in the anterior mediastinum, usually the upper part. In 4 cases the middle mediastinum was also involved. Patient 2 had tumour extending to the anterior chest wall with infiltration into the sternum. All male patients were submitted to testicular ultrasonography and CT of the abdomen to rule out a different primary site of the neoplasm and to study the retroperitoneal space.

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Revised 16 Nov. 1990; accepted 23 Nov. 1990.

Resection was initially always attempted with the aim of obtaining adequate tissue for diagnosis and for debulking. Radiotherapy or chemotherapy followed by consolidation radiotherapy was administered in pure seminoma cases. Mediastinal irradiation was delivered with an average dose of 40 Gy, with fields including the whole area of pretreatment disease. Postoperative chemotherapy was always given to non-seminoma patients. Chemotherapy always included cisplatin and in most patients (11 of 14 treated) it was cisplatin 20 mg/m^2 on days 1–5, vinblastine 6 mg/m^2 on days 1 and 2 and bleomycin 18 mg/m^2 on days 2, 9 and 16, every 3 weeks (PVB). Cisplatin 20 mg/m^2 on days 1–5, etoposide 100 mg/m^2 on days 1, 3 and 5 and bleomycin 18 mg/m^2 on days 2, 9 and 16 every 3 weeks (PEB) was given in 2 patients. A combination of doxorubicin, vindesine and cisplatin was administered in 1 patient (no. 6). Three to four cycles of chemotherapy were usually given.

Levels of alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (β-HCG) were serially followed in all patients to monitor disease and response. Tumour markers were normal or negative in all patients with seminomas. AFP was initially increased in all non-seminoma patients (mean 513, range 150–950 ng/ml); β-HCG was increased in 2 non-seminoma patients (no. 10, 79 ng/ml; no. 15, 230 ng/ml). Complete blood counts and blood chemistries were done before each cycle of chemotherapy or more often if necessary.

The median durations of response and survival were measured from start of treatment (irrespective of the treatment) to 30 October 1989. Survival plots were drawn with the Kaplan–Meier formula [13] and log-rank statistics were used to compare survival curves [14]. The median duration of follow-up for all patients was 64.5 months (5.4 years): 12 months for the 7 dead patients and 63 months for the 8 alive patients (range 42–117), 64.5 months for seminoma and 61.5 months for non-seminoma patients.

RESULTS

Pure seminomas

Of the 9 seminoma patients 5 underwent biopsies and 4 had subtotal resections (Table 2). Of the 4 patients who were partly resected, 2 received irradiation, 1 received irradiation combined with chemotherapy and 1 received PVB. A postsurgical infection at the mediastinoscopic site precluded immediate irradiation in this patient. The patient died of sepsis during profound chemotherapy-induced leukopenia. A complete response was achieved in the 3 evaluable patients of this subgroup. 1 patient treated with radiotherapy alone developed an intrathoracic recurrence which responded to chemotherapy with achievement of a second long-lasting complete response. These initially resected patients are alive and without sign of disease 42, 44.5 and 117 months from start of treatment.

The 5 patients who underwent biopsies only, because of extensive local disease, were given PVB. Mediastinal radiotherapy was then delivered in 3 patients with complete response to chemotherapy. Irradiation was also given in 2 patients with stable disease after chemotherapy. Radiotherapy had no effect in these 2 patients, who developed distant metastases and died within a year.

Overall, 5 of 7 (71%) patients with seminoma treated with chemotherapy attained a complete response. All 6 seminoma patients who achieved complete remission to first-line treatment (4 to combined modality treatment, 1 to radiation followed by chemotherapy and 1 to radiotherapy alone) are still alive and free of disease at a median of 59.5 months from start of treatment

Table 2. Pure seminoma patients

Patient	First-line treatment	Response	Follow-up
1	PVB × 3, RT	CR	Alive, NED at 64.5 mo
2	PVB × 4, RT	CR	Alive, NED at 73 mo
3	PVB × 4, RT	NC	Relapsed in bone and liver; died at 12 mo
4	PVB × 4, RT	CR	Alive, NED at 54.5 mo
5	PVB × 4, RT	NC	Relapsed in the CNS and mediastinum; died at 5.5 mo
6	Subtotal resection; DVP-RT	CR	Alive, NED at 117 mo
7	Subtotal resection; PVB × 2	NE	Died from sepsis at 2.5 mo
8	Subtotal resection; RT	CR	Relapsed in the pleura and mediastinum; PVB × 3; CR; alive, NED at 44.5 mo
9	Subtotal resection; RT	CR	Alive, NED at 42 mo

DVP = doxorubicin, vindesine, cisplatin; RT = radiotherapy; NED = no evidence of disease; CR = complete response; NC = no change; NE = not evaluable; CNS = central nervous system.

(range 42–117) (Table 2). The median survival of patients with seminomas has not been reached; actuarial survival data project that 67% of patients will be alive at 117 months (9.8 years) from the start of treatment (Fig. 1).

Non-seminomas

3 of the 6 patients with non-seminomatous tumours underwent initial radical resection (Table 3). All 6 received chemotherapy: for an inoperable mass in 3 patients or for persistence of elevated serum levels of AFP, involvement of a mediastinal lymph node or development of lung metastases in the 3 patients who had undergone radical surgery. Complete responses were attained in 2 patients (33%) and both of these patients are alive and free of disease at 61.5 and 81 months from start of treatment. 1 of the 2 patients (no. 14) underwent resection of the residual mass after chemotherapy; no viable tumour cells were found on examination of the excised tissue specimen. 3 patients achieved partial response with chemotherapy; all of them died within 36

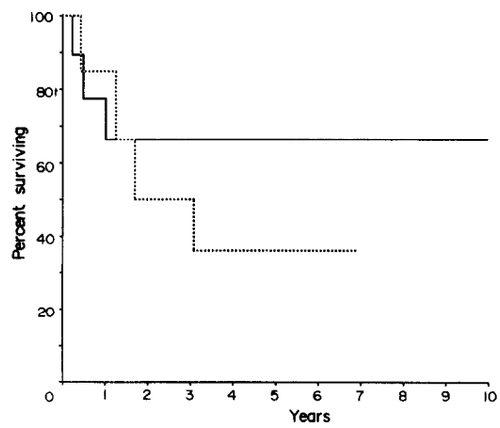

Fig. 1. Survival of patients with pure seminoma (solid line) or with non-seminomatous tumours (dotted line).

Table 3. Non-seminoma patients

Patient	Histology	First-line treatment	Response	Follow-up
10	Seminoma + embryonic carcinoma	Radical resection; relapsed in lung; PVB × 4, DE × 3;	PR	CT*; died at 14.5 mo
11	Yolk sac	Radical resection; increase in AFP; PVB × 4, DE × 5;	CR†	Alive, NED at 81 mo
12	Malignant teratoma	Radical resection; PVB × 4; local relapse; CT‡	PR	Died at 36 mo
13	Malignant teratoma + embryonic carcinoma	PEB × 5	NC	Died at 5 mo
14	Yolk sac	PEB × 3; radical resection	CR	Alive, NED at 61.5 mo
15	Malignant teratoma	PVB × 4	PR	Increase in AFP; DCE × 3; NC; Died at 20 mo

CT = salvage chemotherapy; D = doxorubicin; E = etoposide; C = cyclophosphamide.
*PR lasted 7 months from start of chemotherapy; lung and bone metastases developed and did not respond to cisplatin, cyclophosphamide and methotrexate or to cisplatin and etoposide. †AFP > 400 U/ml, reduced to 32 U/ml after two PVB cycles. ‡Adjuvant chemotherapy was given because of a mediastinal lymph-node metastasis. Local relapse occurred 21 months after surgery and cisplatin and etoposide resulted in PR; chest radiation was then given. An additional local relapse responded briefly to cisplatin, etoposide and ifosfamide.

months from the start of treatment. The only patient who did not achieve a response died in less than 6 months. 3 patients who received second-line chemotherapy attained incomplete and short-lived responses.

The overall median survival time of non-seminomatous patients was 36 months (Fig. 1).

Overall survival

The median survival of all 15 patients with malignant germ cell tumours of the mediastinum has not been reached: 53% of the patients have a projected actuarial survival at 117 months with a plateau reached after 36 months from start of treatment. 8 of 15 patients (53%) are alive at more than 42 months from start of treatment (3.5 years).

Toxicity

In general, surgery was well tolerated in this young group of patients. 2 patients experienced postoperative infections at sites of mediastinoscopy. Another patient had prolonged fever with a pleuropericardial effusion after radical resection. Radiation was also well tolerated. 1 patient suffered severe oesophagitis, however, and another developed pericarditis.

Patients who received chemotherapy commonly experienced nausea and vomiting during cisplatin administration, and alopecia. Marrow suppression was also frequent, and 1 severely leukopenic patient developed an infection at the site of mediastinoscopy with eventual sepsis and death. Neurotoxicity resulted

in a dose reduction of vinblastine in 1 patient with severe paraesthesias, and substitution of etoposide for vinblastine in another patient with an intestinal ileus.

DISCUSSION

Our patients with pure seminomas vs. non-seminomatous tumours of the mediastinum had a different prognosis. The complete response rate was 71% in patients with seminoma and 33% in patients with non-seminomatous tumours. The survival of patients with seminomas was 67%, with a median follow-up of 65 months vs. a median survival of 36 months for non-seminoma patients. The number of patients in this study was small; therefore definite conclusions cannot be drawn. However other investigators have reported similar findings [10]. Although encouraging, the response rate and survival, especially of non-seminoma patients, were poorer than those achieved in advanced testicular tumours, where 84% and 70% of patients with advanced seminoma and non-seminoma tumours, respectively, achieve long-term disease-free survivals [7].

The poor prognosis for patients with mediastinal involvement by malignant germ cell tumours has been reported by several investigators [15, 16]. In a series by Garnick *et al.* [16], patients with retroperitoneal involvement had a better prognosis than those with mediastinal involvement. The poor prognosis of mediastinum as primary site of disease was also noted in a multivariate analysis by Loherer *et al.* [17]. However, the poor results might be at least in part explained by the frequently bulky extension of the disease in these patients; results are in fact similar to those obtained in patients with high-risk germ cell tumours [4, 18].

Within mediastinal germ cell tumours, seminomas appear to be more radiosensitive and probably also more sensitive to chemotherapy than non-seminomas.

The principal treatment of pure seminomas has traditionally been irradiation, although early chemotherapy has been successful in patients with local extension or metastases [19–21]. In a study by Martini *et al.*, 50% of patients with seminomas had a survival time of over 10 years after resection with or without radiation [20]. Similar results were obtained by other investigators [8, 11, 15, 22–26]. In a series from the Memorial Sloan Kettering Cancer Center (MSKCC), 89% of seminomas treated with cisplatin-based chemotherapy had complete responses and were without recurrence at a median follow-up of 29 months [10]. Similar findings were obtained with vinblastine, dactinomycin, bleomycin, cisplatin and cyclophosphamide in combination [15]. These results and our findings challenge the belief that radiotherapy should be the standard treatment for pure seminomas of the mediastinum.

The complete response rate of 33% achieved in non-seminomatous tumours in our series was similar to that reported by other investigators. Although on a small number of patients, the median survival of our patients of 3 years, with 2 out of 6 long-term survivors, is better than that usually reported. Chemotherapy in this setting has a lower efficacy than in testicular tumours and it is unclear whether this is due to the bulky initial presentation of the disease, as suggested by some [18], or to a lower intrinsic biological sensitivity. In a report by Bosl *et al.* of vinblastine/dactinomycin/bleomycin/cisplatin/cyclophosphamide (VAB-6) with surgery, patients with extragonadal non-seminomas had a median survival time of 10.3 months [15]. In the same institution, complete responses were attained in 41% of non-seminomatous patients with extragonadal tumours, with a median surival of 18 months [7]. Survival of non-seminoma patients in an older series from the MSKCC, when treatment consisted of radiation and surgery, was approximately 7 months with only a few long-term survivors [20, 27]. Although comparisons between chemotherapy regimens with or without cisplatin are difficult because of small patient numbers, an advantage of aggressive cisplatin-containing regimens over other types of chemotherapy has been reported [15, 24].

4 of our non-seminomatous tumour patients could be radically resected. This may have influenced the longer survival that we obtained. The importance of surgery before or after chemotherapy in non-seminomatous tumours has been stressed [28, 29]. Because initial resection is seldom able to achieve local control and is difficult, its use should probably be limited to excision of residual masses which might contain viable tumour cells, benign teratoma or necrotic tissue. There is increasing evidence that surgery after cisplatin-based chemotherapy might yield better results than surgery at the onset [2]. Our 2 patients with the best outcomes in the non-seminomatous tumour group had yolk sac tumours, which were either resected before or after chemotherapy. Both patients are without recurrence at 61.5 and 81 months from the start of treatment. Since the number of patients with yolk sac tumours treated with adequate chemotherapy is small, the historically poor prognosis of this subcategory may need to be reassessed [23, 30, 31].

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Eur J Cancer, Vol. 27, No. 3, pp. 277–280, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Structures of the Asparagine-linked Sugar Chains of Human Chorionic Gonadotropin from a Patient with Extragonadal Germ Cell Tumour

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Human chorionic gonadotropin (hCG) purified from the urine of a male patient with extragonadal germ cell tumour contained four asparagine-linked sugar chains in one molecule. The sugar chains were quantitatively released from the polypeptide moiety by hydrazinolysis and recovered as oligosaccharides after *N*-acetylation. The oligosaccharide mixture was separated into a neutral (N) and three acidic (A1, A2 and A3) fractions by anion-exchange column chromatography. By sequential exoglycosidase digestion, methylation analysis and lectin column chromatography, the structures of these oligosaccharides were found to be the same as those of female gestational choriocarcinoma hCGs. Both contain eight kinds of sugar chains: triantennary, abnormal and normal biantennary, and monoantennary complex-type sugar chains with or without a fucosylated core portion.
Eur J Cancer, Vol. 27, No. 3, pp. 277–280, 1991.

INTRODUCTION

HUMAN CHORIONIC GONADOTROPIN (hCG), a glycoprotein produced by the trophoblast, is excreted into serum and urine. Urinary hCG is found not only in normal pregnant women but also in patients with trophoblastic diseases. In hCGs purified from the urine of normal pregnant women [1, 2] or patients with trophoblastic diseases including hydatidiform mole [3], invasive mole [4] and choriocarcinoma [3, 5], structural changes of the asparagine-linked sugar chains are induced in hCG produced by malignant tissues. Although hCG from the hydatidiform mole patient has the same sets of oligosaccharides as normal hCG, that from the invasive mole patient has 2,4-branched triantennary oligosaccharides together with the sugar chains found in normal hCG. In hCGs from the choriocarcinoma patient, abnormal biantennary oligosaccharides are also detected. With this altered glycosylation of hCG, we could successfully discriminate invasive mole or choriocarcinoma hCG from normal pregnancy or hydatidiform mole hCG in an immobilised *Datura stramonium* agglutinin (DSA) column [6].

Although rare, hCG is produced in non-gestational choriocarcinoma-like teratomatous choriocarcinoma. It is important to know whether structural changes also occur in the sugar chains of non-gestational choriocarcinoma hCG. We have therefore studied the sugar chains of hCG purified from the urine of a male patient with a primary extragonadal germ cell tumour of mediastinum.

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Revised 20 Nov. 1990; accepted 23 Nov. 1990.