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Original Paper

Initial Management of Primary Mediastinal Seminoma: Radiotherapy or Cisplatin-based Chemotherapy?

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Primary mediastinal seminoma is an uncommon neoplasm, the optimal management of which is still debated. Radiotherapy produces a 65% disease-free survival rate. We assess whether these results have been improved with the advent of cisplatin-based chemotherapy. Data from 14 patients treated at the Institut Gustave-Roussy were reviewed. 9 had received cisplatin-based chemotherapy (Group 1): their outcome was compared with that of 5 patients treated with radiotherapy without chemotherapy (Group 2). We also reviewed data from the English literature using strict criteria, and report results concerning patients who received cisplatin-based chemotherapy and those who received radiotherapy. 8 of the 9 patients (89%) in Group 1 are long-term disease-free survivors and only 3 of 5 patients in Group 2. The patient who died in Group 1 was the only one who refused surgical resection of residual masses after chemotherapy. The review of the literature revealed that 59 of 68 (87%) patients initially managed with cisplatin- or carboplatin-based chemotherapy and for whom sufficient data are available, are long-term survivors and free of disease. Some of these patients had also received radiotherapy. Only 64 of 103 (62%) treated with thoracic radiotherapy without chemotherapy were long-term disease-free survivors. The disease-free survival rate of 51 patients who received cisplatin-based chemotherapy (excluding those who received carboplatin) was 86%. The difference in survival between patients administered cisplatin-based chemotherapy and those who underwent radiotherapy is apparently not due to unbalanced prognostic factors, the effect of time or non-specific medical management. We conclude that cisplatin-based chemotherapy allows long-term disease-free survival in approximately 85% of patients. These results seem to be higher than those obtained without cisplatin-based chemotherapy. However, a randomised study is required for definitive conclusions, but it is very unlikely that such a study will be performed due to the rarity of this neoplasm. Another alternative would be a meta-analysis based on individual data. © **1998 Published by Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

MEDIASTINAL SEMINOMA is a rare neoplasm involving the anterior mediastinum. It is considered a primary as it is not associated with tumour or scar tissue in the testes, unlike retroperitoneal germ cell tumours (GCTs) [1–3]. The incidence of mediastinal seminoma has been estimated at a quarter of that of primary mediastinal GCTs, whereas the latter account for approximately 2% of tumours of the mediastinum [4, 5]. A mediastinal primary location does not necessarily imply a worse prognosis for seminomas, unlike their non-seminomatous counterparts [6]. However, optimal management of primary mediastinal seminoma is still a subject of controversy. Radiation therapy was a major improvement in treatment at the beginning of the 1970s [7], but it only affords long-term complete remission in approximately 65% of patients [8, 9]. Prompted by the excellent results obtained in testis GCTs, some clinicians have more recently

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introduced cisplatin-based chemotherapy in the management of mediastinal seminomas. However, due to the rarity of this neoplasm, it has not been possible to conduct randomised studies comparing these treatment modalities and most of the series reported so far contain less than 10 patients. Intrigued by these data, we compared our experience of patients initially managed with cisplatin-based chemotherapy to a historical series of patients treated with radiotherapy at the Institut Gustave-Roussy and, then reviewed available data from the literature regarding both treatment strategies.

PATIENTS AND MATERIALS

The Institut Gustave-Roussy (IGR) experience

The records of all patients with mediastinal seminoma registered in a computer database between 1973 and 1995 were reviewed. All histological slides were reviewed by one of us (MJTL). Patients with retroperitoneal nodal involvement were excluded as this site was considered the primary. Initial staging included a biopsy of the tumour, a chest X-ray, meticulous examination of the testes and the abdomen, an ultrasound scan of the abdomen and determination of serum alphafetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH) levels. Since 1980, a computerised tomography (CT) scan of the thorax and the abdomen has also been performed. Survival was calculated from the date of diagnosis to the last date of follow-up.

Compilation of data from the literature

Data from the English literature since 1970 were reviewed. Reports were selected when the following data were available: (1) histologically-proven primary mediastinal seminoma, (2) details on therapeutic management, (3) long-term disease-free survival, (4) separate data for reports including extra-mediastinal primary seminoma or primary mediastinal non-seminomatous GCTs. The largest experience published was selected when there were multiple publications from the same institution.

RESULTS

Primary mediastinal seminomas treated at IGR

14 patients were considered to fulfill the clinical and histological criteria of primary mediastinal seminomas. The median age was 30 years (range 25–62 years). Serum AFP and hCG were normal. No patient had extramediastinal metastasis at presentation. 9 patients received cisplatin-based chemotherapy as first-line therapy at the IGR from 1979 to 1995 (Group 1), whereas 5 patients received radiation therapy without cisplatin-based chemotherapy, from 1973 to 1985 (Group 2).

8 of the 9 patients (89%) in Group 1 are alive and free of disease with a median follow-up of 65 months (Table 1). One patient died of disease progression 18 months after diagnosis. This 62-year-old Moroccan patient received a short course of irradiation at a dose of 1.8 Gy in two fractions for a bulky mediastinal seminoma with a superior vena cava syndrome, followed by four courses of cisplatin–etoposide every 3 weeks. A partial response was obtained, but a residual mass measuring 4 cm in diameter persisted. He refused surgical resection and was again referred, 3 months later, for a histologically confirmed mediastinal and pulmonary relapse. He received three courses of VeIP (combination of vinblastine, ifosfamide and cisplatin) with a minor response (< 50% reduction in volume) and was again lost to follow-up in Morocco, although a further cycle and surgery had been envisaged. He died of progressive disease 9 months later, while undergoing palliative thoracic radiotherapy.

In contrast, only 3 of the 5 patients in Group 2 are alive and disease-free with a median follow-up of 73 months. 2 patients had a recurrent seminoma during the first two years and subsequently died: 1 of progressive disease and the

Table 1. *Results of therapy in patients treated at IGR from* 1973 *to* 1995

	Age (years)	Chemotherapy	Radiotherapy (RT)	Surgery (complete resection)	Response to chemotherapy	Follow-up (months)
Group 1						
1	30	VAB-6×6	40 Gy	ND	cCR	NED 187+
2	27	VAB-6×6	ND	After chemotherapy	pCR	NED 144+
3	25	VAB-6×4	ND	Before chemotherapy	ND	NED 130+
4	27	EP×4	ND	ND	cCR	NED 66+
5	47	EP×4	ND	ND	cCR	NED 65+
6	37	PVB×4	ND	Before chemotherapy	ND	NED 50+
7	27	EP×4	50 Gy	After chemotherapy	pCR	NED 46+
8	25	EP×4	—	Before chemotherapy	—	NED 16+
9	62	EP×4	4 Gy	—	PR	Relapse 3 mo DOD 14 mo
Group 2						
1	25	ND	44 Gy	ND	ND	DOD 12
2	40	ND	44 Gy	ND	ND	Relapse 21 mo Surgery + RT 20 Gy Relapse 27 mo Died of malignant melanoma 36 mo
3	30	ND	40 Gy	ND	ND	NED 73+
4	34	ND	45 Gy	Before RT	ND	NED 164+
5	42	ND	40 Gy	Before RT	ND	NED 125+

VAB-6: cisplatin, actinomycin-D, cyclophosphamide, bleomycin, vinblastine; EP: cisplatin, etoposide; PVB: cisplatin, vinblastine, bleomycin; pCR: histologically-proven complete response after complete surgery; cCR: complete response after chemotherapy alone; PR: partial response; NED: no evidence of disease; mo = month; DOD: died of disease; ND: not done.

other of malignant melanoma. Their outcome is detailed in Table 1.

Review of the medical literature

Data from medical literature are summarised in Tables 2 and 3. 59 of 68 patients (87%) treated with chemotherapy including cisplatin or carboplatin were alive and disease-free with a median follow-up of more than 2 years. If only the 51 patients who received cisplatin-based chemotherapy were considered, excluding the patients who were treated with carboplatin or whose specific platinum drug was not specified, the 2-year disease-free survival was then 86%.

In contrast with these results, only 64 of 103 (62%) patients managed with radiotherapy without platinum-based chemotherapy were alive and disease-free after 2 years of follow-up. These results compare poorly with those achieved with chemotherapy and seemingly cannot be attributed to an effect of the time of treatment, since only 37/66 (56%) and 9/15 (60%) patients treated with radiotherapy in more recent periods, respectively since 1980 and 1985, were alive and free of disease. It is impossible to assess the effect of surgery in this analysis because data are missing in many reports (Tables 2 and 3). Furthermore, the incidence of extramediastinal metastasis at presentation is absent from most of the earlier reports of patients treated with radiation therapy. These data are also missing in more recent reports, or have not been reported separately, indicating whether the primary site of the seminoma is mediastinal or not. The description of staging procedures is lacking in many reports.

DISCUSSION

Comparing treatment groups is always a difficult task and such comparisons are prone to potential biases when performed outside randomised studies. However, when neoplasms are rare the most efficient methodology for an assessment of treatment results is to conduct a historical comparison. The results of a new therapeutic modality are more often than not accepted, when they are confirmed in other institutions, even though definitive validation is awaited. In the present study, we observed a better outcome for patients with primary mediastinal seminoma when managed with cisplatin-based chemotherapy compared with our historical series of patients having received thoracic radiotherapy. Long-term disease-free survival was 89% (8/9) in the

Table 2. Results of treatment of primitive mediastinal seminoma including platinum-based chemotherapy (compilation of data available in the literature)

Author, year, institution [reference]	Number of patients	Radiation therapy	Complete surgery	Regimen	Complete remission	DFS (2 years)
Logothetis, 1985 M.D. Anderson, Houston [10]	4	NR	NR	CISCA II CP	NR	4
Kiffer, 1989 Melbourne [11]	1	NR	NR	PVB	0	0
Glaccone, 1991 Turin [12]	7	6	2	PVB DVP	NR	4
Lemarié, 1992 Tours [13]	13	9	NR	BEP VAB-6 PVB PVBE	10	11
Childs, 1993 Auckland [14]	2	1	NR	PVB BEP	2	2
	5	3	NR	CBDCA	4	4
Gutierrez-Delgado, 1993 Moscow [15]	6	—	NR	VAB-6 PVB BEP CP	NR	5
Mencel, 1994 Memorial Hospital, New York [16]	19	NR	NR	VAB-6 EP VP16-CBDCA VAB-6/EP	NR	18
Goss, 1994 Toronto [17]	8	1	3	BEP VAB-6	8	8
Gerl, 1996 Munich [18]	3	NR	NR	VelP EIP PVB	3	3
Total	68					59 (87%)

DFS: disease-free survival; CISCA II: cisplatin, doxorubicin, cyclophosphamide; PVB: cisplatin, vinblastine, bleomycin; DVP: cisplatin, vindesine, doxorubicin; BEP: bleomycin, etoposide, cisplatin; VAB-6: cisplatin, actinomycin-D, cyclophosphamide, bleomycin, vinblastine; PVBE: cisplatin, vinblastine, bleomycin, etoposide; CBDCA: carboplatin; VP16: etoposide; CP: cisplatin, cyclophosphamide; EP: cisplatin, etoposide; VeIP: vinblastine, ifosfamide, cisplatin; EIP: etoposide, ifosfamide, cisplatin; NR: not reported in the publication.

Table 3. Results of radiotherapy without platinum-based chemotherapy in the treatment of primitive mediastinal seminoma (compilation of available data in the literature)

Author, year, Institution [reference]	Number of patients	Dose (Gy)	Complete surgery	DFS (2 years)
Schantz, 1972, Boston [7]	12	24–60	12	12
Johnson, 1973, M.D. Anderson, Houston [19]	2	NR	1	1
Martini, 1974, Memorial Hospital, New York [20]	8	NR	1	2
Cox, 1975, Washington [4]	6	20–40	NR	4
Medini, 1979, Minnesota [21]	5	34–45	NR	3
Polansky, 1979, Yale [9]	4	37–50	0	3
Raghavan, 1980, Royal Marsden [22]	5	35–45	1	3
Bush, 1981, New Mexico [23]	13	25–60	1	7
Economou, 1982, Baltimore [24]	10	30–58	3	8
Hurt, 1982, Mayo Clinic [25]	16	13–45	6	7
Jain, 1984, Memorial Hospital, New York [26]	7	18–46	7	4
Kiffer, 1989, Melbourne [11]	3	30–37	3	2
Giaccone, 1991, Turin [12]	2	40	2	1
Lemarié, 1992, Tours [13]	2	NR	0	0
Dulmet, 1993, Marie Lannelongue [27]	8	30–60	8	7
Total	103			64 (62%)

DFS: disease-free survival; NR: not reported in the publication.

cisplatin-based CT group, versus 60% (3/5) in the radiotherapy group, the only drawback being that the number of patients is too small to allow firm conclusions. It is noteworthy that the only patient in Group 1 who relapsed and finally died of disease was undertreated because he did not comply with treatment. The review of the literature confirms these results with an 87% 2-year disease-free survival for patients who received cisplatin-based chemotherapy [10–18, 26], contrasting with a 2-year disease-free survival of only 62% for patients who were treated with radiotherapy, but without chemotherapy [4, 7, 9, 11–13, 19–27]. These survival rates of patients managed with radiation therapy are consistent with earlier reports. Before the era of cisplatin, Sterchi and associates reviewed a series of 108 patients managed with radiotherapy with or without surgery and found a 58% overall survival at 5 years [8]. A few years later, Polansky and associates reviewed 103 cases with a 71% disease-free survival [9].

Both retrospective studies and reviews of published series may be biased due to various parameters such as pretherapeutic variables with a prognostic value, cancer treatment modalities other than radiotherapy and chemotherapy, and improvements in medical care during different periods of time. Prognostic factors relative to metastatic seminomas, be they testicular or extragonadal, are not well defined and only the presence of extrapulmonary visceral metastasis was considered relevant for the prognosis in the recent international consensus classification [28]. Metastasis at presentation is infrequent in mediastinal seminoma: in our series, no patient presented with extrapulmonary metastasis, but data were too often lacking in the literature to permit a correct assessment. However, patients who presented with metastasis or with a bulky primary would have been more frequently in the chemotherapy group [13, 14, 29]. This, therefore, could not have biased the comparison against the radiotherapy group. The rarity of metastasis at presentation is also a substantial argument against the potential bias represented by the gradual evolution of staging procedures, including chest CT scan during the more recent period. Other parameters suspected of carrying an adverse prognostic value in mediastinal seminomas include advanced age and the presence of the superior vena cava syndrome [25, 29]. In our series, the mean age did not differ between the two groups and the older patient with superior vena cava syndrome was in fact in the chemotherapy group.

The use of surgery may have also biased the results in our review analysis. Unfortunately, surgical management is not always mentioned in medical reports. However, complete resection seems to have occurred more frequently in patients who received radiotherapy and therefore could not be a bias against this group, since mortality due to surgery is generally low in these young patients. In our series, the number of complete resections was not significantly different between the two groups: 5/9 in Group 1 (chemotherapy) versus 2/5 in Group 2 (radiotherapy). As most patients who received radiotherapy were treated in the 1970s, whereas most of those who received chemotherapy were treated in the 1980s, progress in medical management could have led to another bias. However, this is not the case since disease-free survival of patients who received radiotherapy during the more recent period did not improve. Finally, unpublished results or incomplete data according to the criteria initially required for our analysis may have biased these results [29–37]. These last reports are in accordance with the excellent results of chemotherapy in mediastinal seminomas [32, 33, 35, 38], while some others outline the good local control obtained with radiation therapy [34, 36].

In a retrospective study performed at the Memorial Sloan-Kettering Cancer Center comparing the results of cisplatin-based chemotherapy in extragonadal seminomas to a historical group of patients treated with radiotherapy, Jain and associates

reported similar results to ours: 10 of 11 patients who received chemotherapy were long-term survivors without evidence of disease versus only 5 of 10 patients treated with radiotherapy [26]. One might contend that patients should be treated by initial radiotherapy and be given salvage chemotherapy when relapse occurs. If chemotherapy is effective in the salvage setting, the apparently worst results in disease-free survival in the radiotherapy group may ultimately prove comparable in terms of overall survival. However, the disappointing results obtained with chemotherapy when used as salvage therapy for progression after radiotherapy is a major argument in favour of its use during the initial management of patients with primary mediastinal seminoma [16, 26, 33, 39]. Data are too scant in the literature for an appraisal of the role of carboplatin as opposed to cisplatin in the management of these neoplasms. Investigators from Auckland reported 4 disease-free long-term survivors out of 5 patients treated with carboplatin with or without radiotherapy [14].

Management of postchemotherapy residual mediastinal seminoma is not clearly defined. In patients with testicular seminoma, failure of therapy can be due to the size of the residual mass and surgical resection is recommended in case of a residual mass exceeding 3 cm [38]. Postchemotherapy resection of residual mediastinal seminoma is also recommended by most recent authors [12, 15, 35]. Whatever the size, viable cells or local relapse are found in 10–15% after cisplatin-based chemotherapy for advanced testicular seminoma [38, 40]. In contrast, recurrent extragonadal seminomas seem to occur more often and Gutierrez-Delgado and associates report a relapse rate of 31% in a series of 13 patients [15]. This argues in favour of the extension of surgical indications in mediastinal seminomas after chemotherapy. Another option, recommended by others, is to deliver radiotherapy directly to the residual masses [14]. However, this strategy does not permit a histological appraisal of response to chemotherapy so that subsequent treatment can be correctly determined. Moreover, the potential benefit of radiotherapy for postchemotherapy residual masses has been recently shown to be minimal [41].

In conclusion, on the basis of our own experience and the review of the literature, we recommend the use of cisplatin-based chemotherapy for the initial management of mediastinal seminoma. Like others, we think that chemotherapy ought to be used in a neo-adjuvant setting [12, 14, 15, 26]. Although no consensus exists regarding the choice of the optimal regimen, we would opt for the cisplatin–etoposide combination since its efficacy is widely acknowledged in testicular seminoma [16]. The use of bleomycin in advanced seminoma is debated because of the risk of pulmonary toxicity [42] and the poor results of the vinblastin–bleomycin combination before the era of cisplatin, compared with non-seminomatous GCTs [43]. If bleomycin is used in mediastinal seminoma, the number of cycles should be three instead of four and radiotherapy should be avoided to decrease the risk of toxic pneumonitis. Patients with residual masses should undergo surgery. However, no firm recommendations can be given for small residual masses < 3 cm or complete response to chemotherapy. Some authors advocate systematic surgery or radiotherapy, whatever the size of the residual masses based on a high local relapse rate [15], while others support the close surveillance of patients with computed tomographic scan [38].

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