NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 3• 265–269

Mediastinal malignant germ cell tumours: presentation of 15 cases and literature review

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Primary mediastinal malignant germ cell tumours (PMMGCT) account for 10-15% of anterior mediastinal masses. Given their uncommon occurrence, methods of primary treatment are still to be defined. We present our experience with the PMMGCT patients.
Materials and methods. A retrospective analysis was performed on 15 patients (5 women and 10 men, age: 16-46 years, median age 33 yrs) treated at our institution between 1982 and 2000. This series included four cases of pure seminomas (female counterpart – dysgerminomas), five seminomas along with other components, and six non-seminomas. Thirteen patients underwent surgical procedures, including complete or incomplete resections or excisional biopsy only. All 15 patients received combined treatment consisting of platinum-based chemotherapy, followed by radiotherapy and/or surgical removal of the persistent mass.
Results. Median follow-up time of 6 months (range:1 mo.-17 yrs). Two of 4 patients with seminomas and 2 of 11 patients with nonseminomas are alive and disease-free. Median survival for patients with pure seminomas/dysgerminomas vs. other types was 10 and 47 months, respectively, actuarial 5-year survival 50% vs. 18%, respectively. One patient was lost to follow-up. Two long-term survivors with nonseminomas had complete surgical excision of the mediastinal tumour mass. One patient died due to treatment-related complications (postoperative acute respiratory distress syndrome – ARDS).
Conclusion. Despite progress in multidisciplinary management of PMMGCT, treatment results remain unsatisfactory.

Pierwotne złośliwe guzy zarodkowe śródpiersia: opis 15 przypadków i przegląd piśmiennictwa

Pierwotne złośliwe nowotwory zarodkowe śródpiersia (PZNZŚ) stanowią 10 do 15% guzów w tej lokalizacji. Ze względu na ich rzadkie występowanie nie opracowano jak dotąd standardowej metody leczenia.
Materiały i metody. Przeprowadzono retrospektywną analizę wyników leczenia 15 chorych na PZNZŚ (5 kobiet i 10 mężczyzn w wieku od 16 do 46 lat, mediana 33 lata) hospitalizowanych w naszym ośrodku w latach 1982-2000. W grupie tej były cztery przypadki czystych nasieniaków (u kobiet – rozrodczaków), pięć przypadków guzów mieszanych – nasieniaków z udziałem innych guzów zarodkowych i sześć przypadków nowotworów zarodkowych bez utkania nasieniaka. Zabiegi chirurgiczne pod postacią całkowitego bądź niecałkowitego wycięcia guza, lub tylko pobrania materiału do badania histopatologicznego zastosowano u 13 chorych. Wszyscy chorzy otrzymali leczenie skojarzone z udziałem chemioterapii zawierającej pochodne platyny z następową radioterapią i/lub operacyjnym usunięciem resztkowej masy guza.
Wyniki. Po sześciomiesięcznej medianie obserwacji (zakres od 1 miesiąca do 17 lat) 2 z 4 chorych z nasieniakami i 2 z 11 chorych z nowotworami nienasieniakowymi żyje bez objawów nowotworu. Mediana czasu przeżycia wynosiła, odpowiednio, 10 i 47 miesięcy, a prawdopodobieństwo 5-letniego przeżycia 50% i 18%, odpowiednio, u chorych z czystymi nasieniakami/rozrodczakami i z pozostałymi nowotworami. Jeden chory zginął z obserwacji. Dwaj żyjący chorzy z guzami nienasieniakowymi przebyli doszczętne chirurgiczne usunięcie guza śródpiersia. Jeden chory zmarł z powodu powikłań leczenia (pooperacyjny ostry zespół niewydolności oddechowej).
Wnioski. Przeprowadzona analiza retrospektywna wykazała, że pomimo postępu w wielodyscyplinarnym postępowaniu w PZNZŚ, wyniki leczenia są niezadowalające.

Key words: extragonadal, germ cell tumours, treatment
Słowa kluczowe: pozagonadalne, złośliwe guzy zarodkowe, leczenie

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Introduction

Primary mediastinal malignant germ cell tumours (PMMGCT) comprise approximately 10 to 15% of all adult anterior mediastinal tumours and about 2 to 5% of all adult germ cell tumours [1, 2]. PMMGCT occur more frequently in men than in women. The relative risk of these tumours is increased several hundred-fold in subjects with Klinefelter syndrome and 47, XXY karyotype, but is much lower in mosaic Klinefelter syndrome [3-5]. PMMGCT are known to be associated with 250-fold increased relative risk of haematological malignancies – particularly acute megakaryoblastic leukaemia and myelodysplasia with abnormal megakaryocytes [6, 7]. The relative risk of a second non-germinal and nonhaematological malignancy is comparable to that in patients with primary testicular carcinoma, whereas the risk of developing metachronous testicular cancer is higher [8, 9].

The origin of PMMGCT remains unclear. Recent studies have shown that extragonadal and gonadal germ cell tumours have virtually the same cytogenetic pattern of aberrations. The most common abnormalities include triploid chromosomes, increased number of 12p, i(12p) and tandem duplications within 12p [10,11]. The meiotic midprophase spermatocyte seems to be the precursor of all germ cell malignancies, irrespective of their location. Mediastinal tumours arise from mismigrated transformed primordial germ cells located along the urogenital ridge between the sixth cervical and the second sacral vertebra, whereas gonadal germ cell tumours in men arise in premeiotic spermatocytes [12]. The differences within histological subsets may be explained by cellular environment resulting in phenotype differences.

Before the introduction of platinum-based chemotherapy the prognosis in PMMGCT was extremely poor, with only 3% of patients surviving longer than 16 months [13]. The use of modern cisplatin-based chemotherapy regimens has markedly improved therapeutic outcomes [14-18]. Currently, radiotherapy is reserved for the treatment of pure seminomas/dysgerminomas but as a single modality it provides only approx. 60% of long-term survival [19]. Mediastinal location of PMMGCT is an independent poor prognostic factor regardless of the level of tumour markers or metastatic status [20]. We present our experience with the management of PMMGCT.

Patients and methods

Between the years 1982 and 2000 15 patients with PMMGCT were referred to the Department of Oncology and Radiotherapy, Medical University of Gdańsk, and to the Dept. of Chemotherapy PCK Hspital in Gdynia, Poland. This group consisted of 5 women and 10 men, aged 16-46 years (median 33 years). Symptoms at presentation included chest pain, dyspnoea and non-productive cough in 11 patients, symptoms of superior vena cava syndrome in 7, hemoptysis and weakness in 2 cases each, shoulder pain and weight loss in 1 case each. Gynecomastia was present in one patient with cytogenetically confirmed Klinefelter syndrome, whereas the gonads were normal in all patients on clinical and ultrasound examinations. One patient had clinically apparent metastases to the left supraclavicular lymph nodes. Chest radiography revealed anterior mediastinal mass in all cases, in 3 combined with hydrothorax (in two diagnosed as hemothorax), in 3 – with malignant infiltration of the adjacent pulmonary parenchyma, in 1 – with hilar involvement and in 1 – with pulmonary metastases. Histopathology includeded pure seminoma (female counterpart – dysgerminoma) in 4 cases, 5 cases of seminoma along with immature teratoma, embryonal cell carcinoma, chorioncarcinoma, or teratocarcinoma and 6 pure nonseminomas. Histological diagnosis was established at thoracotomy (4 patients), anterior mediastinotomy (3 patients), sternotomy (6 patients) and CT-guided fine needle biopsy (2 patients). Baseline data included complete blood counts, routine serum chemistries and tumour markers – HCG and AFP. Three of patients with tumours containing elements of embryonal cell carcinoma had elevated AFP levels, whereas HCG levels were elevated in all 7 cases containing elements of chorioncarcinoma. Patients treated in the early eighties didn't have markers evaluated on a regular basis.

Treatment

Standard treatment of PMMGCT at our institution includes surgical excision of the tumour, if feasible, followed by platinum-based chemotherapy, with radiotherapy reserved for pure seminomas, or for palliation of symptoms. Surgical procedures were performed in 13 patients. Of those, complete resection of the mediastinal mass and segmentectomy of the right lung was performed in 1 case, and microscopically and macroscopically incomplete resections – in 3 cases each. The remaining 6 cases underwent excisional biopsy only. In 2 cases of seminoma with components of chorioncarcinoma diagnosis was established by CT-guided fine-needle aspiration biopsy. One of those cases was initially misdiagnosed and treated as non small cell lung cancer. Appropriate treatment was introduced after a partial excision of the tumour had provided final diagnosis.

All patients were offered 1 to 6 cycles of chemotherapy including maximally 4 cycles of platinum-based regimens: classical PVB regimen consisting of cisplatin, vinblastin and bleomycin, BEP consisting of bleomycin, etoposide and cisplatin, or BEP + methotrexate. One patient, who initially refused chemotherapy was offered thoracic irradiation instead. Chemotherapy preceding surgery was administered in 2 patients. Of those, 1 patient received 4 courses of cyclophosphamide, dactinomycin and methotrexate followed by 2 courses of PVB, and 1 received 4 courses of BEP combined with methotrexate. Chemotherapy was given in full-prescribed doses. Seven patients (4 with seminomas, 3 with non-seminomas) received thoracic irradiation for residual tumours after completion of chemotherapy. Radiotherapy was delivered with ^{60}Co photons, using two parallel opposed fields. Total doses ranged from 30 to 45 Gy given in 10 to 25 daily fractions. One patient was given radiotherapy (total dose 20 Gy in 10 fractions) at the time of progression for palliation of symptoms. Surgical removal of residual masses was attempted in 2 cases.

Results

All 15 patients were evaluated for response to treatment and survival (Table I). Median follow up was 6 months (range 1 month to 17 years). Three of 4 patients with pure seminomas partially responded to chemotherapy. Of those, 2 received radiotherapy for the residual mass and are alive and free of disease for 7 and 11 years respectively, and 1 patient relapsed and died after 26 months. The fourth patient completely responded to

Table I. Data on treatment and outcome of all patients

Patient initials	Age/ Sex	Type of tumour	Chemotherapy (No. of cycles)	Radiotherapy /Total dose (Gy)	Overall survival (months)	Treatment outcome
EB	23/F	*Dysgerminoma*	PVB (3)	35	10	Died due to progression
LN	43/F	*Dysgerminoma*	PVB (3)	30	132+	Alive, free of disease
JG	18/M	*Seminoma*	PVB (3)	40	26	Died due to progression
MS	31/F	*Dysgerminoma*	BEP (4)	40	84+	Alive and free of disease
BK	16/M	*Non seminoma*	MAC (5), PVB (4)	45	228+	Alive and free of disease
KG	29/M	*Non seminoma*	PVB (4)	20	10	Died due to progression
GZ	33/M	*Non seminoma*	BEP (4)	No	12	Lost to follow-up
TH	45/M	*Non seminoma*	BEP + M (4)	45	10	Died with no evidence of tumor
AL	18/M	*Non seminoma*	BAMVO (1)	No	4	Died due to progression
TS	40/F	*Non dysgerminoma*	COCA (4)	40	9+	Alive and free of disease
WW	42/M	*Non seminoma*	BEP (2)	No	6	Died due to progression
JN	35/M	*Non seminoma*	BEP (1)	No	2	Died due to progression
GK	38/F	*Non dysgerminoma*	BEP (1)	No	2	Died due to progression
AR	40/M	*Non seminoma*	BEP (1)	No	6	Died due to progression
JR	20/M	*Non seminoma*	BEP (4)	No	96+	Alive and free of disease

Legend: PVB: cisplatin, bleomycin, vinblastine; BEP: cisplatin, etoposide, bleomycin; MAC: methotrexate, adriamycin cyclophosphamide; BAMVO: bleomycin, adriamycin, methotrexate, vinblastine, vincristine; COCA: *cisplatin*, *vincristine*, *cyclophosphamide*, adriamycin
+: patient alive

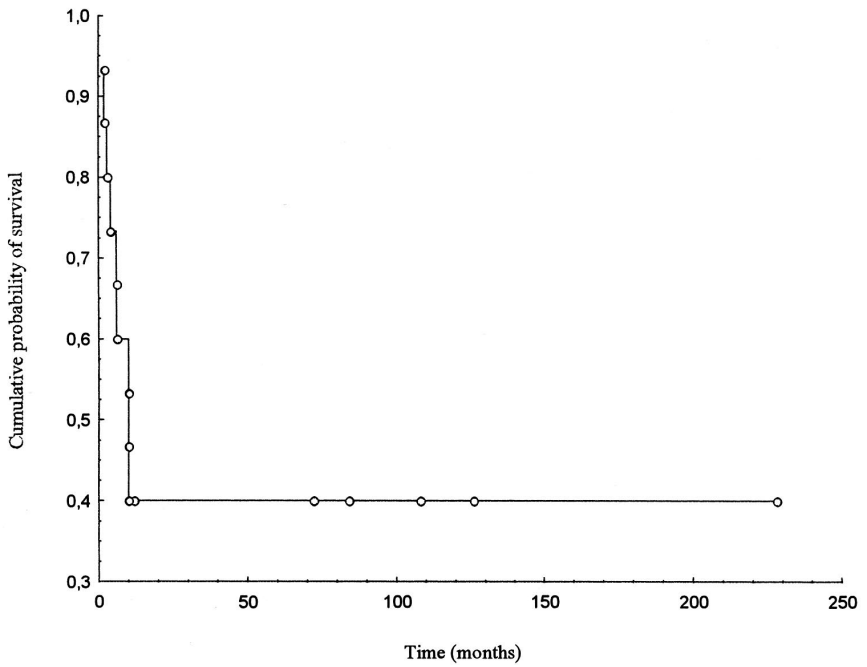

Figure 1. Kaplan-Meier analysis of survival for the entire group of patients

thoracic irradiation alone, but shortly afterwards developed multiple cerebral metastases and died after 10 months.

Of the 11 patients with nonseminomas only 2 are alive and free of disease. Of those, 1 patient underwent complete surgical removal of the tumour mass with normalization of the tumour markers, and then received four courses of BEP chemotherapy. He has remained in complete remission for 9 years. Another patient received 6 courses of chemotherapy followed by thoracic radiotherapy. With normal levels of biochemical serum markers, he was referred for surgical removal of the residual mass 12 months after the completion of irradiation. Histopathological examination of the resected specimen did not reveal viable tumour cells. He has been alive and free of disease for 19 years. One patient who showed clinical, radiological and biochemical partial responded after to 4 courses of BEP+M received subsequent radiotherapy and underwent removal of the persistent mediastinal mass. He died due to postoperative complications (ARDS) 10 months after the diagnosis without evidence of malignancy in the resected surgical specimen. One patient in complete response after incomplete surgery and chemotherapy was lost to follow up. The remaining 7 patients treated with chemotherapy followed by thoracic irradiation developed both local and distant progression and died within 2 to 10 months (median: 5 mos) from the diagnosis. Median time of survival for the entire group of patients was 10 months (Figure 1); 47 and 10 months for seminomas and other pathological types, respectively, whereas actuarial 5-year survival 50% and 18%, respectively.

Discussion

Due to their rarity, therapy of PMMGCT has not been assessed in prospective randomised trials. Patients with PMMGCT are routinely treated with chemotherapy regimens identical to those used in their gonadal counterparts. Bokemeyer et al. [18] have recently published data on 635 PMMGCT patients, 54% of those with primary mediastinal localization, treated at 11 American and European institutions between 1975 and 1996. Their results support the relative efficacy of cisplatin-based chemotherapy followed by complete surgical removal of residual mass. However, the optimal treatment strategies for PMMGCT remain to be defined. Lower treatment efficacy in patients with PMMGCT, as compared to primary gonadal germ cell tumours, has not been explained. It may result from a more advanced stage of the disease at presentation. Unsatisfactory results of treatment presented in this case series support previously published data which has shown that effective chemotherapy and completeness of surgical excision are essential in the management of PMMGCT. Interestingly, none of our patients completely responded to chemotherapy. Similar results were reported [21,22], although there are numerous examples of complete remissions even in patients with massive PMMGCT [2, 22-24]. Bower et al [25] reported excellent results in 16 patients treated with POMB/ACE regimen – 15 complete responses and a 73% 5-year survival. Currently, the role of post-chemotherapy aggressive surgery for residual mass is unquestionable [18, 26]. It should be emphasized that the presence or absence of viable tumor cells is the most important predictor of survival [27] If malignant cells are still present in the resected specimen, additional chemotherapy is usually recommended [24, 25]. Indeed, 2 long-term survivors in our group were treated with timed aggressive surgery following systemic treatment. In contrary, 2 patients ineligible for surgery had the shortest survival. The role of radiotherapy in PMMGCT is less defined. In this series radiotherapy proved ineffective. Generally, this modality is considered useful in pure seminomas/dysgerminomas, but less so in other germ-cell tumours. Hurt et al [28] have reported high local control rate after thoracic radiotherapy with the doses of 30 to 35 Gy followed by a boost dose of 5 Gy for primary mediastinal seminoma. However, 8 patients in this series have died because of distant metastases, and long-term survival was only 52% [28]. Bush et al [29], using doses in the range of 35 to 60 Gy achieved a 69% ten-year survival with a 54% relapse-free survival. Six of 13 patients in that series relapsed within the irradiated volume. Kersh et al [30] reported 100% five-year survivals in a group of 12 patients with primary mediastinal seminomas after radiotherapy doses ranging from 30 to 50 Gy. In contrast, no local control was achieved in 9 patients with nonseminomas and the overall survival was only 8.8%. These results may either question the role of radiotherapy in PMGCT or emphasize the role of precisely performed pathological examination. Some of the „pure seminomas" may in fact contain other histological components. In our series, one patient with mediastinal seminoma achieved complete response after the total dose of 40 Gy, but subsequently he developed cerebral metastases and died within 4 months from diagnosis. One patient with mixed nonseminoma with incomplete response to chemotherapy was administered radiotherapy (45 Gy). Persistent residual mediastinal tumour was later resected, but no viable malignant cells were found in the specimen. However, the patient died due to postoperative complications (ARDS). Another patient managed by chemotherapy followed by radiotherapy and surgical removal of the necrotic mass has been alive and free of the disease for 14 years. This may arise from the addition of radiotherapy to aggressive chemotherapy, although it may well reflect our inability to distinguish small deposits of viable tumour cells from the necrotic tissue. Indeed, in all partial responders to chemotherapy, further radiation up to the total dose of 35 Gy was ineffective. These patients died due to local and distant progression. One may discuss whether the total dose was suboptimal or tumour burden was too big.

Our results support the view that prognosis in PMMGCT differs among histological subtypes, and is better for pure seminomas than for other germ-cell types (50% vs. 18% actuarial 5-year survival). In the former

group the extent of the disease, response to systemic treatment, and histological tumour type in the residual specimen seem to have prognostic value [21,26]. As in gonadal tumours, serum tumour markers are useful in treatment monitoring. Normalising levels during chemotherapy correlate with remission, whereas elevated levels strongly suggest persistent disease. Unfortunately the lack of regular measurements of serum tumour markers in our patients has rendered such analysis impossible.

In conclusion, PMMGCT are rare tumours with unfavourable prognosis. Cases with pure seminomatous histology with no bulky disease may be effectively treated with definitive radiotherapy. All other histological subtypes and bulky seminomas should be managed with cisplatin-based chemotherapy followed by radical resection of residual mass. In case of persistent malignancy in the resected specimen further chemotherapy is mandatory.

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Paper received: 9 December 2002
Accepted: 11 March 2003