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Analysis of treatment results in primary germ cell tumours with mediastinal location: own experience

Analiza wyników leczenia pierwotnych nowotworów z komórek rozrodczych o lokalizacji w śródpiersiu — doświadczenia własne

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Abstract

Introduction: Primary germ cell tumours with mediastinal location comprise 1–6% of mediastinal tumours and 2–5% of all germ cell tumours occurring in adults. They are identified mostly in the 3rd decade of life, in 90% of cases in men. The most common symptoms are dyspnea, chest pain, cough, fever and weight loss.

The aim of the present study was the analysis of our own results of treatment of primary germ cell tumours with mediastinal location, and a review of the literature concerning this subject.

Material and methods: Five patients (4 males, 1 female) median age 27.8 years (range 23–30 years) treated in the period from 1999 to 2009 in Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Lung Cancer and Chest Tumours in Warsaw, due to germinal tumours with primary mediastinal location, entered the study.

Results: All patients received chemotherapy according to the BEP regimen. All patients achieved an objective response to treatment. Two patients died due to disease progression in spite of II- and III-line treatment. Three patients are still in follow-up. The median survival time was 55.8 months (range 8.0–120.0 months).

Conclusions: Primary mediastinal germ cell tumours have worse prognosis than do those with gonadal location. Based on our observations and review of the literature, it can be concluded that the results of treatment of non-seminoma type germ cell tumours with primary mediastinal location remain poor. Patients who develop early recurrence or progression during first-line chemotherapy are particularly at risk of unfavourable outcome. Identification of new standards of treatment in tumours resistant to cisplatin require further studies evaluating the effectiveness of new generation cytostatic drugs.

Key words: germ cell tumours, mediastinum, chemotherapy, radiotherapy

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Streszczenie

Wstęp: Pierwotne nowotwory z komórek rozrodczych o lokalizacji śródpiersiowej stanowią 1–6% guzów śródpiersia oraz 2–5% wszystkich nowotworów z komórek rozrodczych występujących u dorosłych. Rozpoznawane są najczęściej w 3. dekadzie życia, w 90% u mężczyzn. Najczęstsze objawy to: duszność, bóle w klatce piersiowej, kaszel, stany podgorączkowe i utrata masy ciała. Celem pracy była ocena wyników leczenia pierwotnych nowotworów z komórek rozrodczych o lokalizacji śródpiersiowej i przegląd piśmiennictwa poświęconego tej tematyce.

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Materiał i metody: W okresie od 1999 do 2009 roku w Klinice Nowotworów Płuca i Klatki Piersiowej Centrum Onkologii-Instytut im. Marii Skłodowskiej-Curie w Warszawie leczono 5 chorych z nowotworem z komórek rozrodczych o pierwotnej lokalizacji śródpiersiowej, 4 mężczyzn i 1 kobietę. Średnia wieku wyniosła 27,8 roku (zakres 23–30).
Wyniki: U wszystkich chorych zastosowano chemioterapię według schematu BEP. U wszystkich chorych uzyskano obiektywną odpowiedź na leczenie. Dwóch chorych zmarło z powodu progresji choroby pomimo stosowania chemioterapii II i III linii. Trzech chorych nadal pozostaje w obserwacji. Mediana czasu przeżycia wyniosła 55,8 miesiąca (zakres 8,0–120,0).
Wnioski: Pierwotne nowotwory z komórek rozrodczych o lokalizacji śródpiersiowej są nowotworami o rokowaniu gorszym niż w lokalizacji gonadalnej. Na podstawie obserwacji własnych i przeglądu piśmiennictwa można stwierdzić, że wyniki leczenia pierwotnych nienasieniaków w lokalizacji śródpiersiowej pozostają niezadowalające. Szczególnie niekorzystne są wyniki leczenia chorych, u których dochodzi do wczesnej wznowy lub progresji w trakcie chemioterapii I linii. Określenie nowych standardów postępowania w nowotworach opornych na cisplatynę wymaga dalszych badań oceniających skuteczność cytostatyków nowych generacji.

Słowa kluczowe: nowotwory z komórek rozrodczych, śródpiersie, chemioterapia, radioterapia

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Introduction

Primary germ cell tumours with mediastinal location constitute 1–6% of tumours of the mediastinum, and approximately 2–5% of all germ cell tumours in adults. They are the most frequent extragonadal tumours [1, 2]. The second extragonadal location in respect of prevalence is the retroperitoneal area; other extremely rare locations include the hypophysis, pineal body, liver and lung [2]. Germ cell neoplasms are usually diagnosed in the third decade of life, in 90% of cases in men [3]. Tumours located in the mediastinum are usually symptomatic. The most frequent symptoms are dyspnea, chest pain, cough, low grade fever and weight loss [4]. The most important diagnostic procedures are: computed tomography of the chest (chest CT) and determination of serum tumour markers concentration — the β subunit of human chorionic gonadotropin (βHCG) and alpha-fetoprotein (AFP). Prior to treatment, attempts should be made to identify the histopathological type of tumour. The material for diagnosis is obtained with the help of invasive methods, such as transbronchial biopsy and, rarely, mediastinoscopy or thoracotomy.

Taking into account their morphology, germ cell tumours are divided into two groups: seminomas and nonseminomas. Nonseminomas are heterogeneous neoplasms; they include *teratoma maturum* and *teratoma immaturum*, yolk sac tumour (YST) also known as endodermal sinus tumour (EST), embryonal carcinoma, chorioncarcinoma and mixed germ cell tumours (MGCT) [5]. In the case of nonseminomas, elevated βHCG serum level is found in 30–50% of patients, whereas AFP — in 60–80% of patients [3]. In the case of seminomas, only βHCG serum level is elevated.

According to the International Germ Cell Cancer Cooperative Group (IGCCCG), based on histopathological diagnosis, serum tumour markers level, location of primary lesion and the presence and location of metastases, patients are classified into one out of three prognostic groups. In the case of seminoma, the patient is classified into either the group with good or with medium prognosis. In the case of mediastinal non-seminoma, the patient is classified into the group with poor prognosis, irrespective of the levels of tumour markers [6]. Therapeutic procedures in the treatment of nonseminomas include cisplatin-based chemotherapy, and in the case of lack of complete remission — surgical removal of residual lesions.

The objective of the study

The objective of the study was to analyse the results of treatment in primary germ cell tumours with mediastinal location in patients treated in the Lung Cancer and Chest Tumours Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw. Our own results were compared with the literature concerning this subject.

Material and methods

During the period from 1999 until 2009, at the Lung Cancer and Chest Tumours Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw, five patients (4 men and 1 woman), mean age 27.8 years (range 23–30 years), with germ cell tumour with primary location in the mediastinum, were treated.

Four patients were diagnosed with pure endodermal sinus tumour — EST (Fig. 1); in one case MGCT (EST, embryonal carcinoma and

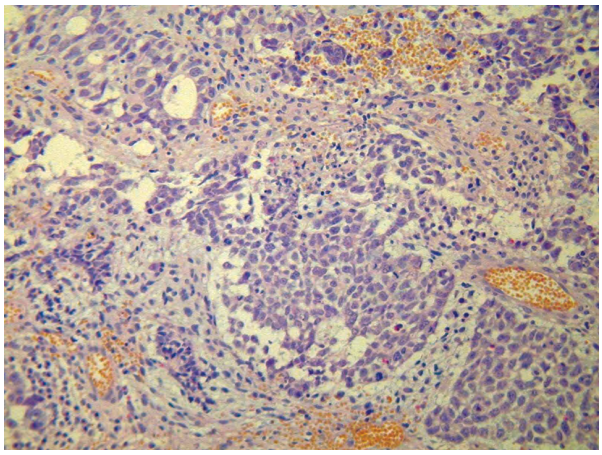

Figure 1. *Endodermal sinus tumour* (EST) with mediastinal location

Rycina 1. Fragment utkania *endodermal sinus tumour* (EST) o lokalizacji śródpiersiowej

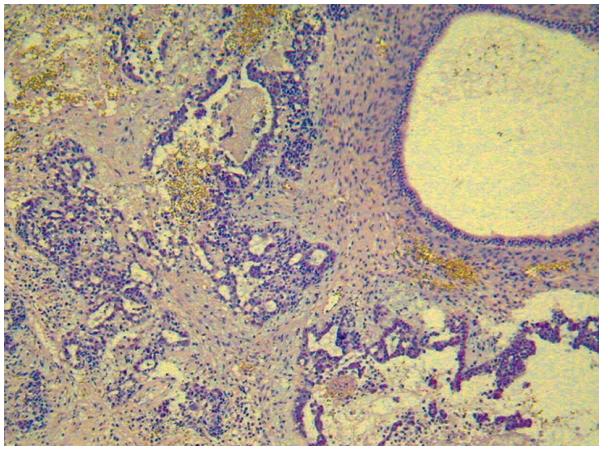

Figure 2. *Mixed germ cell tumor* with mediastinal location (*teratoma and embryonal carcinoma*)

Rycina 2. *Mixed germ cell tumor*. Wycinek z guza śródpiersia. Widoczne są fragmenty utkania *teratoma* i *embryonal carcinoma*

teratoma) was diagnosed (Fig. 2). In all of them, significantly elevated AFP concentration (range 469 — 58390 IU/mL) was found. Elevated βHCG was noted in one patient only (MGCT). According to Karnofsky's scale, all patients had good or very good performance status. All patients were diagnosed using spiral chest CT and/or magnetic resonance and surgical biopsy. Gonadal location of neoplasm was excluded in all of them. Due to primary mediastinal location of germ cell tumour, all patients were classified into the group with poor prognosis.

The clinical characteristics of the study group are presented in Table 1.

Results

The patients received chemotherapy, combined with surgical treatment in some of them. The summary of therapeutic methods was included in Table 2. All patients achieved an objective response to treatment. Two patients died due to disease progression, and three patients are still in follow up. The median survival time was 55.8 months (range 8.0–120.0).

Due to the small number of patients, a brief description of the treatment used in individual subjects has been presented below.

The first patient underwent operation on 8th February, 2008 — resection of tumour (type RX). Diagnosis of EST was made. Since March, 2008, the patient has received 6 cycles of BEP regimen (bleomycin, etoposide, cisplatin). Complete response (CR) was achieved (Figs 3, 4). The patient received second look surgery on 18th of June, 2008. No living cancer cells were found. In September, 2008, disease progression (PD) was found (elevat-

Table 1. Patients' clinical characteristics

Tabela 1. Charakterystyka kliniczna chorych

Patient	Sex	Age	Diagnosis	KPS	AFP (IU/mL) AFP level	βHCG (mIU/mL) βHCG level	Surgical treatment
1	M	30	EST	100	20318	0.1	YES RX
2	M	28	EST	100	20209	0.1	YES R1
3	K	29	EST	80	58390	0.9	NO
4	M	29	EST	100	469	0.1	YES R0
5	M	23	EST + *carcinoma embryonale* + *teratoma maturum*	80	1217	42028	NO

EST — Endodermal Sinus Tumour; KPS — Karnofsky's Performance Status; AFP — α-fetoprotein; βHCG — the β subunit of human chorionic gonadotropin

Table 2. Treatment and response rate

Tabela 2. Leczenie i uzyskane odpowiedzi

Patient	Treatment	n	Treatment response	Reoperation	Pathological response	Progression free survival (months)	Second line of chemotherapy	Third line of chemotherapy	Radiotherapy	OS (months)
1	BEP	6	CR	Yes	CR	3	VBL+IFO+DDP	OXL+PXL+GCB	Yes	19
2	BEP	4	CR	Yes	CR	–	–	–	No	60
3	BEP	6	CR	Yes	CR	3	VeIP	–	Yes	120
4	BEP	4	PR	Yes	CR	–	–	–	No	72
5	BEP	3	PD	No	–	2	TIP	–	Yes	8

BEP — bleomycin, etoposide, cisplatin; VBL — vinblastine; IFO — ifosfamide; DDP — cisplatin; VeIP — etoposide, ifosfamide, cisplatin; TIP — paclitaxel, ifosfamide, cisplatin; OXL — oxaliplatin; GCB — gemcitabine; PXL — paclitaxel; RTH — radiotherapy; CTH — chemotherapy

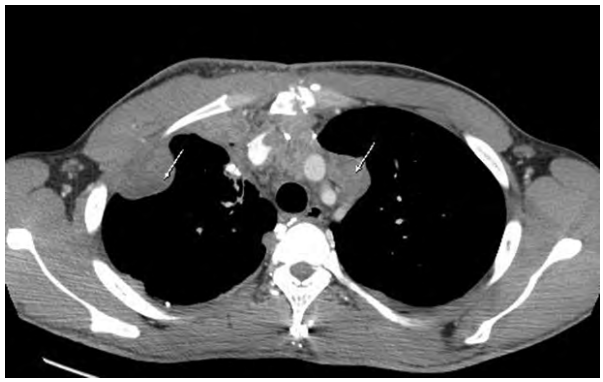

Figure 3. Chest CT with contrast before chemotherapy (mediastinal neoplasia with pleural infiltration — marked with arrows)

Rycina 3. KT KLP z kontrastem przed chemioterapią (masy nowotworowe w śródpiersiu oraz guzowaty naciek opłucnej — strzałki)

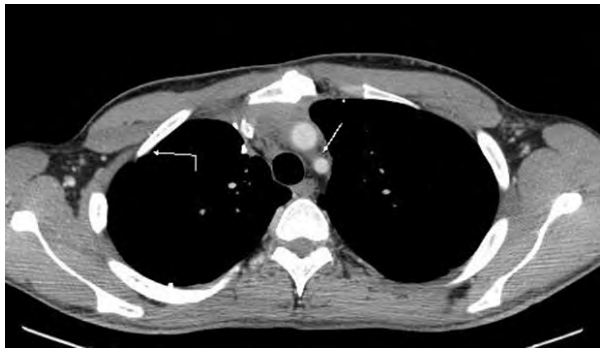

Figure 4. Chest CT with contrast after chemotherapy (complete regression)

Rycina 4. KT KLP po chemioterapii (całkowita regresja zmian)

ed AFP and recurrence in the chest). The patient was qualified to second-line treatment according to the following regimen: vinblastine 8.25 mg *i.v.*/m^2 + ifosfamide 2400 mg *i.v.*/m^2 + cisplatin 40 mg *i.v.*/m^2. Treatment was discontinued after administration of two cycles in November, 2008, due to PD. Subsequently, the patient was qualified to rescue chemotherapy (CHT) based on oxaliplatin, paclitaxel and gemcitabine. After 4 cycles of CHT, in March, 2009, treatment was stopped due to PD. Palliative irradiation to the mediastinal area (20 Gy/4Gy) was performed. In September, 2009, further progression was found. The patient received symptomatic treatment only and died in November, 2009.

The second patient underwent surgery in January, 2008 — right-sided thoracotomy with removal of tumour, and medial lobectomy (type R1). Diagnosis of EST was made. In February, 2008, significantly elevated AFP was noted (20209 IU/mL). Chest CT revealed disease progression. In March, 2008, the patient started chemotherapy with BEP regimen. The treatment was complicated by neutropenic fever requiring hospitalisation. Four cycles of BEP were given, each of which was complicated with neutropenia and thrombocytopenia. In June, 2008, the patient underwent second look surgery — no living cancer cells were found. The patient is in still follow-up, with no features of active neoplastic disease.

The third patient, female, underwent mediastinoscopy in January, 1999. She was diagnosed EST. In February, 1999, due to disease progression in the mediastinum and lungs, and elevated AFP (58 390 IU/mL), the patient began chemotherapy according to the BEP regimen. Six cycles were given with radiological partial response (PR) and normalisation of tumour markers. No clinically significant haematological and non-haematological complications were observed. In August, 1999, thoracotomy was performed, residual lesions in the mediastinum were removed and bypass of the superior vena cava was performed. The pathological examination revealed only features of necrosis; no neoplastic cells were found. Four

weeks after the operation, AFP concentration increased to 220 IU/mL with no signs of radiological PD. Second-line treatment according to the VeIP regimen (etoposide, ifosfamide, cisplatin) was started. On the second day of chemotherapy, the condition of the patient deteriorated. Right-sided hemiparesis occurred. Computed tomography of the brain revealed the presence of two metastatic sites. The patient received palliative whole brain radiation (30 Gy/10 fr.). Due to complete remission in the chest confirmed by 99mTcMIBI scintigraphy, and normalisation of tumour marker levels, the patient was qualified to brain radio-surgical treatment. A 13 Gy single dose was given, using rotary technique with 5 arches and 1 isocentre. The treatment was ended in March, 2000. The patient is in still follow-up; she is in a good performance status with no biochemical or radiological features of PD.

The fourth patient underwent surgery on 12th June, 2008 — left-sided thoracotomy with removal of tumour mass. Pathological diagnosis was EST. Due to elevated AFP (469 IU), CT was performed, which showed local recurrence with no distant metastases. Four cycles of chemotherapy according to the BEP regimen were given, radiological PR was achieved and normalisation of the markers levels were obtained. No significant haematological or non-haematological toxicity of treatment was observed. The patient underwent second look surgery — no neoplastic cells were found, only areas of fibrosis and hyalinisation with foci of necrosis. The patient is still in follow-up; he is in a very good health condition with no signs of active disease.

The last patient had mediastinoscopy performed in 2008; MGCT (*carcinoma embryonale* with elements of EST and fields of *teratoma maturum)* was diagnosed. Radiological examination of the chest revealed numerous metastatic lesions. AFP concentration was 1217.8 mIU/mL and βHCG was 42028 mIU/mL. The patient was qualified to chemotherapy according to the BEP regimen. Treatment was complicated with anaemia grade 2 requiring a red blood cells concentrate transfusion, and neutropenia grade 4 with no signs of neutropenic fever (G-CSF was administered as a prophylaxis). After two cycles of chemotherapy, a decrease in the level of the markers (AFP — 30.8 mIU/mL; βHCG — 784.2 mIU/mL) and radiological regression of the lesion in the mediastinum was achieved. After the third cycle of BEP chemotherapy, the βHCG level increased to 930 mIU/mL (with no radiological signs local PD). The patient was qualified to second-line treatment according to the TIP (paclitaxel, ifosfamide, cisplatin) regimen. Four cycles of second-line chemotherapy were given. A slow decrease of βHCG concentration was observed. When chemotherapy was completed in July, 2009, neurological symptoms occurred (left-sided hemiparesis, disequilibrium), so brain CT was performed showing multiple metastatic lesions in the brain and cerebellum. The patient received palliative whole brain radiation (20 Gy/5 fr.). A slight improvement in general health status was achieved, but the patient died 4 weeks later.

Discussion

Current recommendations concerning treatment of patients with primary nonseminomatous germ cell tumours of the mediastinum suggest a multidisciplinary approach [7]. Due to the location of such tumours, the patients are classified into the group with poor prognosis (according to the IGCCCG). It is recommended to give 4 cycles of chemotherapy according to the BEP regimen, and then, if the level of the markers is decreased (examination 4 weeks after the last chemotherapy), the patient is qualified to thoracotomy in order to remove residual lesions. In the case of lack of complete regression, and when an objective response was achieved, it is possible to continue chemotherapy for up to 6 cycles. In the case of progression during treatment or recurrence of the disease, it is recommended to start second-line chemotherapy.

We have presented our own results and a review of the literature concerning the strategy of a therapeutical approach and prognostic factors in patients with diagnosed primary nonseminomatous germ cell tumours with mediastinal location.

Prognostic factors

In the published analysis of 635 patients with extragonadal location of germ cell tumours, primary nonseminomatous tumours of the mediastinum were diagnosed in 287 patients [8]. The aim of the analysis was to determine prognostic factors. The patients with seminomas had very good prognosis (89% of patients achieved five-year survival). In the population of patients with diagnosed mediastinal nonseminoma, 65% and 45% of patients survived 2 and 5 years, respectively. Better prognosis was seen in the patients with retroperitoneal location (two- and five-year survival was achieved in 76% and 62% of patients, respectively). The tumour type was considered the most significant prognostic factor.

An additional analysis allowed four prognostic groups to be distinguished. Classification into the group depended on the obtained number of points. The evaluation concerned the presence of liver and lung metastases, elevated βHCG (1 point each) and the presence of mediastinal location and CNS metastases (2 points each). In the group of patients with nonseminomatous germ cell tumours, the best prognosis concerned the patients who received 0–1 point, whereas the worst — those who received > 3 points (five-year survival rates were 69% and 17%, respectively) [8]. It was thought that the factors that influence poor prognosis were mediastinal location and the presence of metastatic lesions at initial diagnosis, and the location of metastatic disease in the central nervous system was considered especially unfavourable [8].

The best prognosis concerned the patients > 29 years of age, without metastatic disease and without elevated levels of βHCG. The proportion of five-year survivals in this group was 84% [8]. Among the described patients treated at the Lung Cancer and Chest Tumours Department, two patients met the above-mentioned criteria. In both cases, standard chemotherapy allowed radiological partial response to be achieved with normalisation of the markers. After chemotherapy, the patients underwent thoracotomy with removal of residual lesions in the mediastinum. Both patients are still in follow-up and in very good general health condition (currently 60 and 120 months after diagnosis).

Surgical treatment

Surgical treatment constitutes an integral part of the therapy of patients with primary mediastinal germ cell tumours located in the mediastinum. In the case of normalisation of the level of the tumour marker concentrations after chemotherapy, in patients with no distant metastases, it is recommended to remove residual lesions. Evaluation of postoperative specimens is crucial for prognosis.

In patients with the presence of distant metastases, clear recommendations have not been made [7].

It is important to measure the level of the markers just before consecutive cycles of chemotherapy, and 4 weeks after chemotherapy is completed. Such a policy allows for reliable judgement of the dynamics of the disease [6]. In the case of normalisation of tumour marker levels or persistently elevated values in two consecutive examinations made at the interval of 4 weeks, surgical treatment is recommended. If more than 10% of "viable" neoplastic cells are found in surgical specimens, two cycles of supplementary chemotherapy are applied [6]. The increase of tumour marker concentrations during chemotherapy or immediately after it is completed is an indication for second-line chemotherapy.

The analysis of the results of treatment of 158 patients with primary mediastinal non-seminomas was published [9]. The operation was performed 4–5 weeks after the last cycle of chemotherapy (which allowed regeneration of bone marrow and evaluation of the level of the markers). The operation consisted in resection of residual lesions together with adjacent structures (usually infiltration concerned the pericardium — 74%, the lung — 55% and the phrenic nerve — 30%). In some cases it was necessary to carry out vascular reconstruction. Perioperative complications were seen in 23% of patients, including 6% of deaths. Histopathological examination of residual lesions usually showed the presence of necrosis and teratoma (60%), and in the remaining patients — persistent germ cell tumours, sarcomas and cancers. In some cases, no correlation was found between the results of postoperative pathological examination and the levels of the markers (in 50% of patients with residual neoplastic tissue, the levels of AFP and βHCG before the operation were low).

The best prognosis was seen in the patients in whom the postoperative specimen examination revealed only necrosis. The prognosis was 6 times worse for the patients who developed teratoma and 15 times worse for the patients with the malignant neoplasm [9]. An independent negative prognostic factor was elevated levels of the markers found after the operation. Similar results have been shown by Kesler and Sakurai [10, 11].

Neoplastic cells were not found in residual lesions in any of the patients of the Lung Cancer and Chest Tumours Department who underwent surgery after first-line chemotherapy. Nevertheless, two patients developed a rapid recurrence of the disease (in one case — a massive local recurrence occurred 2 months after the operation, in the second case — metastases to the CNS occurred 6 weeks after the surgery).

Surgical procedures are a separate issue in the treatment of mediastinal germ cell tumours. Tumour biopsy is recommended prior to treatment, to determine the histopathological type of the tumour. It is not recommended to remove the whole lesion for diagnostic and therapeutic purposes because such a strategy deteriorates prognosis [10].

In the material from the Lung Cancer and Chest Tumours Department, in three cases, diagnosis was made based on evaluation of the whole

tumour removed during thoracotomy. The extent of the operation was influenced by a lack of preoperative diagnosis. In one case there were also some difficulties connected with obtaining a correct histopathological diagnosis – the initial diagnosis was thymoma. Immunohistochemical analysis and evaluation of the markers typical of germ cell tumours are very helpful for diagnosis [6].

Second-line treatment

Approximately 80% of patients with primary germ cell tumours located in the mediastinum benefit from first-line cisplatin-based chemotherapy [12]. In the remaining patients, resistance to cisplatin (PD during 4 weeks after chemotherapy completion) or complete resistance to cisplatin (PD during treatment) is observed [13]. Life expectancy for patients in whom PD occurred during or shortly after cisplatin-based chemotherapy is poor. It has been shown in the published analysis of treatment results of 164 patients with germ cell tumours (17% with mediastinal location) that independent negative prognostic factors were: time to progression < 2 years after chemotherapy completion, lack of CR, and high levels of the markers found at the moment of recurrence (AFP >100 mIU/mL, βHCG >100 mIU/mL) [14]. Among the patients with three negative prognostic factors, only 7% survived for 2 years. In second-line treatment, chemotherapy according to the VIP, TIP or VeIP regimens is used as a rule [7]. It allows objective response to be achieved in 30-40% of patients [6]. Due to the limited efficacy of cytostatic drugs applied to date, research is being conducted in order to determine the efficacy of other therapeutical options. Most publications have concerned oral forms of etoposide, paclitaxel, gemcitabine and oxaliplatin. In phase II studies, 20% of objective responses to treatment with gemcitabine were obtained in patients with recurrent or cisplatin-refractory primary mediastinal germ cell tumours [15, 16]. Similar results were obtained using monotherapy with oxaliplatin [17]. In a phase II study of 35 patients that evaluated the efficacy of a two-drug regimen (gemcitabine plus oxaliplatin), in second-line treatment, 46% of objective responses with the median survival of 13 months were achieved [18]. In a study that evaluated the efficacy of a three-drug regimen (paclitaxel, gemcitabine and oxaliplatin) in a group of 41 patients with recurrent germ cell tumour resistant to cisplatin, 51% of objective responses, including 15% of complete responses, were achieved [19].

Another therapeutical strategy for patients with recurrent germ cell tumours may be high-dose chemotherapy with autologous stem cell transplantation. Published initial results are encouraging in respect of treatment of patients with recurrence and patients with mediastinal non-seminomas, for whom this strategy was applied as a first-line treatment [13]. Unfortunately, despite the encouraging results of phase II studies, until now we do not have positive results of randomised clinical trials, which could change the standards of treatment.

Among the patients treated at the Lung Cancer and Chest Tumours Department, progression of the disease after first-line chemotherapy occurred in two cases; in one case, progression in the form of elevated markers occurred during chemotherapy. Second-line therapy according to TIP and VeIP, and GOP regimens were used. No responses to second line treatment were observed.

Metastases to the central nervous system

The factor that significantly deteriorates prognosis for patients with germ cell tumours is the presence of metastases to the CNS. This problem concerns 2–3% of patients [20]. An analysis conducted on 198 patients allowed three prognostic groups to be distinguished [21]. The first group included patients with lesions in the CNS observed at the moment of diagnosis. The second group included patients with isolated recurrence in the CNS. The third group included patients with both systemic and CNS recurrence. The proportion of two-year survival for groups 1, 2 and 3 was 57%, 44% and 22%, respectively. Clear recommendations concerning treatment of CNS metastases have not been made. However, it seems that chemotherapy followed by CNS radiotherapy might improve prognosis [21]. In the above mentioned publication, combined treatment was used most frequently (129 patients out of 198). It consisted of chemotherapy with removal of residual lesions located outside the brain followed by radiotherapy and/or surgical treatment of lesions in the CNS. Independent negative prognostic factors were diagnosis of *chorioncarcinoma*, lack of combined treatment and the presence of multiple lesions in the CNS [21]. Combined treatment of patients with metastatic lesions in the CNS is the only chance to prolong survival.

Due to the fact that sometimes patients after CNS radiotherapy have survived for many years, special attention should be paid to the risk of radiation-induced complications. Neurological disorders may occur months, and even years,

after completion of treatment [20]. They include a wide spectrum of symptoms: memory disorders, motor disorders including ataxia, and personality changes. There have also been cases of secondary neoplasms of the CNS induced by irradiation, and progressing, multifocal leukoencephalopathy, which was finally the cause of death [20].

In the materials from our department, among patients with primary mediastinal nonseminomas, metastases to the CNS were found in two cases. In both patients, they became clinically evident during active treatment. One female patient received palliative radiation to the CNS, and then residual brain lesions were removed using radiosurgery. The patient has been in follow-up for 10 years, with no features of recurrence of the disease and with no late complications of applied treatment. The second patient received palliative radiation to the CNS; slight improvement in his general and neurological health was achieved, but he died 4 weeks afterwards, and the disease dissemination to the CNS has been considered as a direct reason for treatment failure.

Observation after treatment

Patients who have completed treatment due to primary mediastinal germ cell tumour require intensive oncological supervision. It is recommended to determine systematically (every 2 months during the first year, then every 4 months during the second year, and every 6 months during the successive years of observation) the level of the markers and to perform imaging examinations [7]. In patients with this type of tumour, recurrence of the disease may occur even many years after treatment. It is also important to take into account the risk of the occurrence of secondary neoplasms, among others metachronous testicular cancer (accumulated risk amounts to 10%, and it is higher in patients with primary nonseminomatous tumours with retroperitoneal location) [6]. A dependence between mediastinal germ cell tumours of nonseminomatous histology, and increased frequency of haematological neoplasms, especially acute megakaryocytic leukaemia, and more rarely myelodysplasia, histiocytosis or mastocytosis, was described [22]. Chromosomal aberrations typical of primary mediastinal germ cell tumours (12p) were found in blasts, which presumes a common progenitor cell for the two proliferations [23]. Haematological proliferations occur usually during the 6 months after diagnosis of a germ cell tumour, and prognosis for this group is poor, with a predicted mean survival time of approximately 5 months [22].

Conclusions

Primary germ cell tumours of the mediastinum are neoplasms with worse prognosis than that for tumours with gonadal location. Patients with diagnosed primary mediastinal germ cell tumours constitute a heterogenic group in respect of morphology of tumour, clinical course and prognosis. This paper has presented patients treated at the Lung Cancer and Chest Tumours Department in Warsaw. The used combined treatment allowed complete remission of lesions to be achieved (also in a female patient with metastases to the lung, found at the moment of diagnosis, and metastases to the CNS that manifested themselves during second-line chemotherapy). The surviving patients have been in follow-up for 11 years, 3 years and 18 months from the moment of diagnosis of the disease. Two patients died due to progression of the disease, despite several lines (2 and 3) of applied chemotherapy. One patient died (22 months after diagnosis) due to progression of the disease in the chest, and another patient died (8 months after diagnosis) due to PD in the CNS.

Based on our own observations and a review of the literature, we conclude that the results of treatment of primary non-seminomas with mediastinal location remain unsatisfactory. The results of treatment of patients who developed early recurrence or progression during first-line chemotherapy are especially unfavourable. In order to determine new standards of treatment of cisplatin-resistant neoplasms, further research to evaluate the efficacy of new generation cytostatic drugs is required.

Conflict of interest

The authors declare no conflict of interest.

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