Review Article

Mediastinal germ cell tumours: where we are and where we are going—a narrative review

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Objective: In this review, we summarize the current state of the art of primary mediastinal germ cell tumours (PMGCTs) and we highlight challenges and future research directions for this disease.

Background: PMGCTs account for 1–3% of all germ cell malignancies and for 15% of adult anterior mediastinal cancers. In 60–70% of cases PMGCTs are represented by nonseminomatous germ cell tumours (GCTs), and in 30–40% of cases by seminomas. Even if PMGCTs share histological and biochemical characteristics with gonadal GCTs, they have peculiar clinical and biological features. Nonseminomatous PMGCTs have a poor prognosis, with a 5-year overall survival (OS) rate of 40–50% after platinum-based chemotherapy and surgery, and a long-term OS of only 10% after salvage treatment. Due to the rarity of this disease, no level 1 evidence is available from randomised trials for PMGCTs. The combination of bleomycin, etoposide, and cisplatin (BEP) or etoposide, ifosfamide and cisplatin (VIP) for 4 cycles are recommended as first line treatment options for nonseminomatous PMGCTs. Surgery of the residual disease after chemotherapy is fundamental in the treatment of nonseminomatous PMGCTs. PMGCTs have high TP53 pathway gene alterations, while targetable gene alterations are rarely identified, thus challenging the advance of precision medicine in this field.

Methods: We performed a narrative review of international literature published in English on PMGCTs, focusing the attention on clinical trials, international guidelines and translational studies.

Conclusions: Treatment of patients with PMGCTs is challenging and should be performed in experienced centers. International collaborations should become a priority to ensure optimal patient management. Clinical investigation of new therapeutic options remains an important unmet clinical need, and inclusion of patients in clinical trials should be encouraged. Liquid biopsy is a new promising strategy in PMGCTs.

Keywords: Primary mediastinal germ cell tumours (PMGCTs); extragonadal germ cell tumours (EGCTs); nonseminoma; seminoma

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Introduction

Primary mediastinal germ cell tumours (PMGCTs) account for 1–3% of all germ cell malignancies and for 15% of adult anterior mediastinal cancers (1). The anterior mediastinum represents the most common primary site (50–70%) of extragonadal germ cell tumours (EGCTs), followed by the retroperitoneum (2). EGCTs can be found in the midline structures from the pineal gland to the coccyx (2). During embryologic development, primordial germ cells originate near the allantois of the embryonic yolk sac endoderm; by

the fifth week, these cells migrate through the mesentery to the gonadal ridge and eventually form the gonads (3). The most accepted hypothesis for the PMGCTs origin is that germ cells stop during their migration and remain in the anterior mediastinum, becoming malignant (1,4).

In 60–70% of cases PMGCTs are represented by nonseminomatous germ cell tumours (GCTs), and in 30–40% of cases by seminomas (1,2,5). Mature teratoma is the most frequent among PMGCTs (2).

PMGCTs share histological and biochemical characteristics with gonadal GCTs, as well as the gain of isochromosome (i) 12p (1,2). However, they are characterized by peculiar clinical and biological features, such as a higher frequency of the yolk sac tumour subtype, Alfa-fetoprotein (AFP) secretion and TP53 alterations compared to the gonadal counterpart (6).

The aim of this narrative review is to summarize the current state of the art of PMGCTs and to highlight future directions of research in this challenging field.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-21-33/rc).

Clinical features

The mean age at diagnosis of PMGCTs is 25–35 years (1,7). An association with Klinefelter syndrome (47XXY) is described for nonseminomatous PMGCTs (2,8).

Patients with PMGCTs are most commonly symptomatic at diagnosis, with the most frequent symptoms represented by dyspnea, chest pain, and cough (9). Fever, weight loss and fatigue may also be present (9). In case of elevated beta-human chorionic gonadotrophin (B-hCG), patients may have gynecomastia. Superior vena cava syndrome is present in no more than 10% of cases (1). Less common presentations include chest wall or cervical mass, hemoptysis, hoarseness, nausea, and dysphagia (9). Various causes of mediastinal masses, including mediastinal lymphoma, thymoma, as well as thymic carcinoma, sarcoma, and mediastinal goiter, should be considered as differential diagnoses (10).

AFP and B-hCG can guide the diagnosis, and therefore they should always be measured when an anterior mediastinal mass is found (1). Of note, the significant elevation of tumour markers with a serum B-hCG >1,000 U/L and/or any elevation of AFP support the diagnosis of GCTs without the need of a confirmatory biopsy (2). This is of utmost importance in those cases where urgent start of treatment is required.

Mediastinal germ cell tumours and hematologic malignancies

The development of hematologic malignancies with an aggressive clinical course, mainly acute megakaryoblastic leukemia and myelodysplastic syndromes, has been observed in patients with PMGCTs (9), with a short interval between the diagnosis of GCTs and the hematologic disease. In a retrospective analysis including 287 consecutive patients with PMGCTs the incidence rate of leukemia was 6% (11). Considering both the short time interval between the diagnosis of the two malignancies and the cytogenetic findings with a high incidence of i(12p) in leukemic blasts, it was postulated that PMGCT and the hematologic malignancy may arise from a common progenitor cell. This hypothesis was further supported by a recent study tracing the clonal evolution of neoplasms from a cohort of 15 patients with PMGCTs and hematologic malignancies, which showed that both conditions developed from a shared ancestral clone (12). Of note, shared mutations in *TP53* were present in 91% of patients with PMGCTs and hematologic malignancies, and activating mutations in *KRAS* and *NRAS* in 63% of patients.

Prognosis

The unfavourable characteristics of nonseminomatous PMGCTs have led to the classification of these tumours as a poor prognosis subgroup according to the International Germ Cell Cancer Collaborative Group (IGCCCG), regardless of metastatic extent or tumour marker levels (13). In fact, nonseminomatous PMGCTs exhibit a 5-year overall survival (OS) of 40–50% after platinum-based chemotherapy (CHT) and surgery (2,14). Unfortunately, the long-term OS of patients who relapse after cisplatin-based CHT is only 10%, and therefore dismal (2).

In the recent IGCCCG-Update Consortium analysis of metastatic nonseminomatous GCTs, 3.7% of patients had a primary mediastinal location (15). In accordance with the original classification, the presence of primary mediastinal tumour (HR 2.68, 95% CI: 2.04 to 3.53) and the presence of non-pulmonary visceral metastases (HR 6.6, 95% CI: 4.62 to 9.46) were the most important negative prognostic factors in the new developed final prognostic model, which

also identified a new cut off of lactate dehydrogenase (LDH) 2.5× upper limit of normal, increased age, and presence of lung metastases, as additional prognostic factors (15).

In contrast with nonseminomatous PMGCTs, mediastinal seminomas have a 5-year OS of approximately 90% (2,9,16). In the recent IGCCCG-Update Consortium analysis of advanced seminoma, 2.9% of patients had primary mediastinal tumour (17). Results from this study confirmed the relevance of the IGCCCG classification of seminoma GCTs and suggest LDH at a cut off of 2.5× upper limit of normal as an additional adverse prognostic factor (17). Other variables, including an extragonadal primary tumour, did not add significant prognostic information in good prognosis patients once LDH elevations were considered (17).

Treatment strategies

First line treatment

Due to the rarity of this disease, no level 1 evidence is available from randomised trials for PMGCTs (6).

The combination of bleomycin, etoposide, and cisplatin (BEP) for 4 cycles is recommended as a first line option of treatment for nonseminomatous PMGCTs (1,13). However, considering that the risk of lung toxicity associated with bleomycin may be particularly harmful in patients with a mediastinal mass, who may also require extensive surgery after CHT, caution should be taken by repetitive lung function assessments and/or replacing bleomycin with ifosfamide (6).

Mediastinal seminoma should be treated with 3 or 4 cycles of BEP, depending on the prognosis (good or intermediate) (1).

A study from the Indiana University, evaluating a total of 158 patients who underwent post-CHT surgery for nonseminomatous PMGCTs, showed nine perioperative deaths due to respiratory failure and nine cases of postoperative respiratory failure (18). None of the 17 patients who had received CHT regimen without bleomycin experienced pulmonary complications. These considerations motivated the Indiana University group to support 4 courses of etoposide, ifosfamide and cisplatin (VIP) followed by surgery as the preferred first line option for nonseminomatous PMGCTs (2).

In a phase II study testing the combination of paclitaxel, ifosfamide, and cisplatin (TIP) as first-line treatment for patients with intermediate- and poor-risk GCTs, 16/60 (27%) patients had PMGCTs (19). In the entire population, estimated 3-year progression-free survival (PFS) and OS rates were 72% (poor risk, 63%; intermediate risk, 90%) and 91% (poor risk, 87%; intermediate risk, 100%), respectively (19). However, all five deaths registered in the study occurred in patients with nonseminomatous PMGCTs and the percentage of patients alive at last follow up in this subgroup was 62%, which is similar to the historically results achieved with 4 cycles of BEP or VIP (19). Of note, the cause of death in two of the five patients was a secondary malignancy, represented by a spindle cell sarcoma and an acute myeloid leukemia. In the latter case, molecular analysis identified (i)12p, consistent with a common origin with the GCT rather than from treatment-induced leukemia.

Patients with PMGCTs usually represented a small subgroup of patients in clinical trials evaluating up-front high dose CHT (HDCT). Twenty-eight patients with nonseminomatous PMGCTs were enrolled in a German multicenter trial evaluating first-line sequential high-dose VIP CHT followed by autologous peripheral blood stem cell transplantation (20). Nineteen out of 28 patients remained disease-free; 11 with HDCT alone and eight with additional surgery (20). The 2-year PFS and OS rates were 64% and 68%, respectively (20). Based on these results, the authors suggested a 15% survival improvement compared to data from an international database analysis including patients with mediastinal nonseminoma treated with conventional CHT (16).

According to some experts, data regarding up-front HDCT are not sufficient to suggest this strategy in routine clinical practice, however this treatment modality may be considered for selected patients with nonseminomatous PMGCTs and negative prognostic features, after an accurate discussion with the patient (1).

Another approach tested to improve outcomes in patients with poor risk GCTs is treatment intensification based on early tumour markers decline (21). In a phase 3, multicentre, randomised trial, patients with an unfavourable decline after one cycle of BEP were randomized to BEP (Unfav-BEP) or a sequential dose-dense regimen comprising two cycles of T-BEP-Oxaliplatin with G-CSF support followed by 2 cycles of cisplatin, bleomycin, and ifosfamide with G-CSF support (Unfav-DoseDense) (21). Less than 30% of enrolled patients had nonseminomatous PMGCTs. In the entire population PFS favoured the Unfav-dose-dense arm versus the Unfav-BEP arm (HR, 0.66, 95% CI: 0.44–1.00; P=0.05). No significant interaction was

found between prognostic factors qualifying for poor-risk, including primary site (mediastinal versus testis/retroperitoneal) and PFS. However, patients with a testis or retroperitoneal primary and those with non-pulmonary visceral metastases benefited more numerically (21). Based on this consideration, the authors suggested that patients with a nonseminomatous PMGCTs may not benefit from the dose-dense regimen, even if the low number of patients hinders a firm conclusion. According to the ESMO Consensus Conference, in contrast to other types of poor prognosis nonseminomatous GCTs, the benefit of early CHT intensification for patients with an unfavourable decline in tumour markers is less clear for nonsemimomatous PMGCTs (6).

The role of surgery

First line treatment surgery may be considered as the first therapeutic approach for mature teratoma without marker elevation or other malignant germ cell tumour components. There is no role for CHT in teratoma unless in case of elevated tumour markers (1,2).

Surgical intervention has a role in what is known as 'growing teratoma syndrome', characterized by a growing mediastinal mass which causes cardiopulmonary deterioration precluding completion of the CHT plan in the presence of declining tumour biomarkers (2). Various series on growing teratoma syndrome in GCTs showed that surgical treatment, even if technically challenging, may be curative, and local recurrence may be related to incomplete resection (22,23).

Surgery of the residual disease after CHT is a fundamental component of the treatment of nonseminomatous PMGCTs and every effort should be made in order to obtain a complete resection (1). The main aims of the surgery are to remove CHT-resistant residual of disease and to assess the response to CHT.

Surgery is usually reserved to nonseminomatous PMGCTs with normalized level of tumoral markers, however it has been suggested that also patients with one site of disease and elevated markers after CHT may benefit from surgery (2). Considering that after CHT the residual disease rate is high and that the chemo-sensitivity of PMGCTs is lower compared to the gonadal counterpart, primary surgery or early surgery after one to two cycles of CHT in patients with localised disease may be considered instead of the classical sequence used in metastatic nonseminomatous GCT (i.e., completion of CHT plan followed by resection of residual disease) (6).

Salvage treatment

No clear evidence supports the use of a specific treatment in the salvage setting for PMGCTs, due to the low number of patients included in clinical trials and retrospective series (1).

Different from gonadal GCTs, which can still be cured with salvage treatment, the prognosis of patients with nonseminomatous PMGCTs that relapse after first line treatment is poor. In a retrospective study of 142 patients with nonseminomatous EGCTs, of whom 79 with PMGCTs, treated at eleven European and American centers between 1975 and 1996 and relapsed after cisplatin-containing regimens, 19% of patients were long- term disease free after a salvage treatment (24). Median follow-up since start of salvage treatment was 11 months (range, 1 to 157 months) for all patients and 45 months (range, 6 to 157 months) for surviving patients. Long-term disease free was lower for PMGCTs than for primary retroperitoneal disease, as it was 11% and 30%, respectively (24). Among the nine patients out of the 79 with PMGCTs remaining disease-free, three had received oral etoposide as subsequent salvage treatment, followed by surgical resection of residual the tumor masses. Primary mediastinal site (HR =1.9, 95% CI: 1.2 to 3.0) and lack of sensitivity to cisplatin (HR =2.4, 95% CI: 1.1 to 5.2) were significant negative prognostic factors at both univariate and multivariate analyses for OS (24).

HDCT followed by a bone marrow transplant was first investigated at Indiana University in 1986 and bone marrow transplantation was replaced by peripheral-blood stem cells transplantation in 1996 (25). A retrospective analysis on patients with mediastinal (n=22) and retroperitoneal (n=37) nonseminomatous GCTs, treated with second-line HDCT from the European Group for Blood and Marrow Transplantation (EBMT) showed a 3-year disease free survival and OS rate of 14% for patients with primary mediastinal tumour (26). The median OS was 11 months for PMGCTs and 28 months for patients with retroperitoneal disease. Carboplatin/etoposide-based HDCT was the most frequent regimen reported. Treatment-related deaths occurred in three patients with primary mediastinal tumour after HDCT due to an acute respiratory distress syndrome (n=1), pneumonia (n=1) and mediastinal hemorrhage (n=1) (26).

In a retrospective analysis by Indiana University,

including 364 consecutive patients with relapsed metastatic GCTs treated with HDCT and peripheral blood stem cell transplantation between 2004 and 2014, 20 patients had PMGCTs (25). All patients with PMGCTs had nonseminoma histology. The two-year PFS rate for patients with nonseminomatous PMGCTs versus testicular/retroperitoneal primary sites were 23% (95% CI: 7% to 43%) and 63% (95% CI: 57% to 68%; P<0.001) (25). Primary mediastinal tumor site was among the negative prognostic factor for PFS at the multivariable analysis, along with the use of HDCT as third-line or later therapy, platinum-refractory disease, nonseminoma histology, intermediate or poor risk disease per IGCCCG criteria, and B-hCG ≥1,000 mIU/mL at initiation of HDCT (25).

Challenges in the managements of PMGCTs and future directions

Management of PMGCTs is challenging and should be performed in highly experienced centers, considering that successful CHT and surgery of the residual disease significantly influence survival outcomes. An analysis from the National Cancer Database, including patients with seminoma and nonseminomatous GCTs, showed that increased hospital GCTs case volume was associated with significant differences in survival outcomes, in particular for more advanced disease (27). Hospitals were classified by case volume as high (99th percentile, ≥26.1 cases annually), high-intermediate (95–99th percentile, 14.6–26.0 cases annually), intermediate (75–95th percentile, 6.1–14.5 cases annually), low-intermediate (25–75th percentile, 1.8–6.0 cases annually), and low (25th percentile, <1.8 cases annually). Defining a threshold for high volume centers for PMGCTs is challenging, considering the rarity of the disease. However, it is likely that those centers with strong experience in GCTs treatment and high surgical expertise may offer the best treatment plan also to those patients affected by this rare disease.

Particular caution should be adopted to avoid unnecessary CHT delays or doses reduction of cisplatin or etoposide in the first line setting, which have been associated with inferior outcomes (28). Considering the poor outcomes of nonseminomatous PMGCTs in the salvage setting, every effort should be made to achieve cure by the right first line treatment (6). High surgical expertise is also a fundamental requirement for the proper management of these patients. When HDCT with autologous stem cell reinfusion is considered, the patient should be treated in high volume centers with competence in the field (28). However, the threshold for what is high-volume has not been clearly defined (29).

Considering the rarity of PMGCTs, producing clinical evidence for treatment recommendations is difficult and the inclusion of patients in clinical trials is crucial and should be highly encouraged as well as the sharing of experience and outcomes within international collaborations. Given the importance of referral to experienced centers, every effort should be done to offer equal access to treatment as well as patient consultation done by experts in GCTs.

If the multidisciplinary management of PMGCTs is challenging even in developed nations, additional difficulties are present in low-middle income countries, including delayed presentation, higher proportion of treatment discontinuation, poor follow-up and limited access to salvage treatments such as HDCT (30). Therefore, collaboration between different international centers from different countries should become a priority for the management of patients with PMGCTs, not only for the treatment of patients but also to spread medical education in this field.

In contrast to many other oncological diseases, that have seen a revolution from the approval of targeted treatment and immunotherapy, such advances have been until now unsuccessful in GCTs. Various trials tested angiogenesis inhibitors with poor results (1). Pazopanib showed a partial response of only 4.3% in a phase II trial and only a short period decline of tumour markers (31). Unfortunately, disappointing results with immune checkpoint inhibitors were reported in trials enrolling patients with advanced GCTs, including a phase II study of pembrolizumab (32) and a phase II study (APACHE) of durvalumab alone or the combination of durvalumab-tremelimumab (33). Notably, in the APACHE study, so called hyper progression features were observed in eight cases (72.7%) with durvalumab alone and in four cases in with durvalumab-tremelimumab (36.4%). The APACHE study included 2 patients with nonseminomatous PMGCTs treated with durvalumab-tremelimumab and both experienced hyper progression of disease (33).

Clinical investigation of new therapeutic options remains an important unmet clinical need in the field of GCTs and especially of PMGCTs. The lack of druggable molecular drivers represent a limitation for the advancement of precision medicine in this field (34). In a recent study genomic profiling was performed on a series of 44 patients with nonseminomatous PMGCTs and was compared

Table 1 Major challenges in primary mediastinal germ cell tumours

Challenges	Possible solutions
Rare disease with scarce evidence on treatment recommendations	• Referral to highly experienced centers • Inclusion in clinical trials
Additional difficulties in low-middle income countries	• International collaborations • Medical education programmes
Disappointing results with immunotherapy and targeted treatment	• Inclusion in clinical trials (i.e., basket trials) • Extensive study of the biology of the tumours
High rate of cisplatin-resistance and poor outcomes	• Early identification of TP53 alterations and cisplatin resistant tumours (i.e., through liquid biopsy) • Development of clinical prognostic models

to series of patients with chemo-refractory metastatic seminoma (n=22) and nonseminoma or mixed (n=86) testicular GCTs (34). Nonseminomatous PMGCTs were found to have higher *TP53* pathway gene alterations (P<0.0001) and *PIK3CA* pathway gene alterations (P<0.0001), while cell-cycle pathway gene alterations were lower (P=0.0004). Other targetable gene alterations were rarely identified in PMGCTs, including *BRAF* (n=3, 6.8%), *ERBB2*, *NTRK1*, *MTOR* and *TSC1* gene (n=1, 2.3% all cases). Even if the study did not reveal high frequencies of targetable gene alterations, there may be some opportunities for targeted therapies for selected patients in the contexts of clinical trials, such as with agents targeting *PI3K* pathway or the other rare genes alterations identified (*BRAF*, *ERBB2*, and *NTRK1*). In this context, the inclusion of patients in basket trials should be encouraged. Considering that the interpretation of multigene sequencing reports may be even more challenging in rare diseases, discussion of the results within a molecular tumour board is advised.

A study that identified the association between *TP53* mutations and deletions and cisplatin resistance, found a significantly higher rate of these alterations in nonseminomatous PMGCTs compared to gonadal primary nonseminomas (69% *vs.* 5%) (35). Integrating *TP53* gene alterations may be useful in studies evaluating clinical prognostic models of PMGCTs (34), that could inspire trials evaluating dose-escalation strategies in patients with the worst prognosis.

Liquid biopsy represents one of the most exciting research fields in GCTs with potential implications also in primary mediastinal tumours (36). A recent paper showed significant molecular heterogeneity when comparing the mutational landscape of primary and metastatic pairs from 50 GCT patients, with 68% discordant somatic mutations (37). Considering these data, liquid biopsy may play a role in monitoring, with a non-invasive method, the evolutionary pattern of molecular alterations during and after treatment. Alterations in *TP53*, which were identified in nine cisplatin-resistant patients, were clonal and shared among primary-metastasis pairs (37). Considering that *TP53* alterations could be detected through analysis of plasma cell-free DNA, this may represent a useful approach to allow early identification of patients unlikely to respond to standard chemotherapy. Both seminoma and nonseminoma GCTs express high levels of circulating specific miRNAs, including miR371 (38). While plasma miR375 is highly expressed in patients with teratoma, miR371 was found to be undetectable in teratoma-only patients (38). A recent study demonstrated that miR371-miR375 integrated evaluation may be clinically useful to predict GCT components, which could be of great importance in the context of post-CHT residual disease or other equivocal clinical scenarios to avoid risk of over-treatment or under-treatment (38). Major challenges regarding the treatment of PMGCTs and possible solutions are summarized in *Table 1*.

Conclusions

Management of PMGCTs is challenging and should be performed in experienced centers. Nonseminomatous PMGCTs exhibit poor prognosis with an OS of 40–50% after platinum-based CHT and surgery. The OS drops dramatically to only 10% after salvage treatment. Strong collaborations among experienced centers should become a standard to ensure equal access to treatment and the optimal management of patients. Clinical investigation of

new therapeutic options remains a huge unmet clinical and inclusion of patients in clinical trials should be encouraged. Liquid biopsy is a promising strategy in equivocal clinical scenarios and microRNA biomarkers may have a potential utility also for patients with PMGCTs.

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Footnote

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