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Editorial

POMB/ACE Chemotherapy for Mediastinal Germ-cell Tumours

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MEDIASTINAL GERM-CELL tumour is a facinating disease in terms of its association with haematological disorders, the presence of specific chromosomal abnormalties, and the occurrence of non-germ-cell evolution of the histological pattern. Patients with germ-cell mediastinal tumours have benefitted from the progress of cisplatin-based chemotherapy as have those patients with testicular cancer [1]. However, tumours of mediastinal origin still portend a rather poor prognosis.

The report by Bower and associates (see pages 838–842 of this issue) is interesting because it shows particularly good therapeutic results and addresses the most important questions concerning mediastinal germ-cell tumours. 16 patients are reported, 4 of whom had bulky mediastinal seminoma. No conclusion can be drawn from the seminoma patients: 1 died of treatment, 1 of disease progression, and 2 have no evidence of disease. As mentioned above, only a few cases of patients treated by chemotherapy have been reported in the literature: 37 patients in total, 28 of whom are long-term NED (no evidence of disease) patients (76%) [3]. These results must be compared to those reported with radiotherapy. In a review of the literature, Aygun and associates found 64 patients who have had surgical biopsy or incomplete exeresis followed by radiotherapy: 34 patients are NED (53%) [4]. Conversely, the patients who had complete resection of the primary tumour had a greater chance of cure: there were 12 NED patients in a group of 15 patients who had only complete surgical exeresis of the tumour without any further treatment, and 12 NED patients in 13 patients in whom surgery was followed by mediastinal radiotherapy. It may be concluded that chemotherapy is preferable to radiotherapy in bulky mediastinal seminoma, but that the surgical resection of disease may play a role in the treatment strategy.

However, there are insufficient data from which to conclude the best course of action when residual tumour is found on histological examination of secondarily resected tumour, or the role of postchemotherapy radiotherapy.

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Results of the treatment of non-seminomatous mediastinal germ-cell tumours are more consistent in this series. 12 patients received the POMB/ACE regimen (platinum, vincristine, methotrexate, bleomycin/actinomycin, cyclophosphamide, etoposide). All 12 patients had a CR (complete remission) and all had surgical exeresis of residual tumour after chemotherapy (necrotic debris: 5 patients, mature teratoma: 5 patients, active disease: 2 patients). 3 patients relapsed and died of disease progression, 1 experiencing acute myeloid leukaemia. The 5-year overall survival was 73% (95% confidence interval 42–90%).

These results compare very favourably with previously published data. A compilation of the literature recently showed a 44% long-term NED rate in this tumour [3]. Only a few series have comprised a homogeneous group of patients treated by the same regimen of chemotherapy. It is noteworthy that no report on the results with BEP (bleomycin, etoposide, cisplatin) have been published. Only several cases of patients treated by the BEP regimen are mentioned in different series by Berruti (6 patients) [5], Nichols (10–20 patients) [6], Vogelzang (6 patients) [7] and Fizazi (12 patients) [8].

Bukowski reported on 16 patients who received an alternated regimen of chemotherapy (cisplatin, vinblastine, bleomycin/etoposide, bleomycin, doxorubicin, cisplatin) [9]. There were 4 CRs to chemotherapy only, 6 pCRs (complete resection of non-active residual disease) and 3 sCRs (complete exeresis of residual active disease). The overall 2-year survival rate was approximately 60. Logothetis reported on 4 NED patients in a group of 8 patients treated by the CISCA II regimen (cisplatin, doxorubicin, cyclophosphamide) alternated or not with VB4 (vinblastine, bleomycin) [10].

These results are slightly inferior to those observed in advanced, non-seminomatous, germ-cell testicular tumours. The 2-year overall survival is generally 70–80% in testicular tumours [1].

Thus, primary mediastinal germ-cell tumours have been considered to have poor-risk characteristics: they fit the same prognosis as advanced testicular tumours in the Indiana Classification [1] and in the recently developed International Consensus Prognostic Classification [11].

Conversely, it has been well established that primary retroperitoneal tumours have the same prognosis as their testicular counterparts when similar tumour burdens are considered [12]. It is thus interesting to specifically study prognostic factors of extragonadal germ-cell tumours. An international prognostic study conducted by C. Bokemeyer (Tübingen, Germany) is on-going and may lead to the definition of specific prognostic characteristics in these tumours.

Results of POMB/ACE, shown by Bower and associates, are better than those reported in any other published series. However, these results are consistent with those reported by the same group with this regimen in testicular germ-cell tumours [13]. Hitchins reported the results of POMB/ACE in 193 patients who were treated between May 1977 and February 1988, 20 of whom had an extragonadal primary. 71 patients were retrospectively assigned to the advanced disease group of the Indiana University Prognostic Classification and 121 patients to the large and very large-volume prognostic groups of the Royal Marsden Hospital Classification. The 5-year overall survival rates were 75% and 80% in these 2 groups, respectively. Moreover, an independent study in 41 patients of the large and very large-volume groups of the Royal Marsden Hospital Classification demonstrated a 65% 5-year overall survival rate [14]. It appears that the POMB/ACE regimen of chemotherapy may be a good alternative to BEP in the treatment of mediastinal germ-cell tumours. Chemotherapy must be combined with surgical exeresis of residual disease.

It is noteworthy that neither in this series nor in other papers have active salvage chemotherapy regimens been reported [6]. Moreover, high-dose chemotherapy with haematopoietic stem-cell support has been shown to be inactive as salvage treatment [15].

Other interesting aspects of mediastinal germ-cell tumours concern their biology. The most important observation is that mediastinal germ-cell tumours have the same karyotypic abnormalities as testicular germ-cell tumours. Chaganti and associates performed the karyotypic analysis of 202 germ-cell tumours, 30 of whom were mediastinal primaries [16]. The non-random chromosonal changes were essentially the same. The most important finding is the presence of an isochromosome of the short arm of the chromosome 12. These authors concluded that mediastinal germ-cell tumours may be derived from gonadal lesions. However, the frequent occurence of mediastinal germ-cell tumours in men with Klinefelter syndrome [17] strongly argued against the gonadal origin of mediastinal germ-cell tumours since Klinefelter syndrome patients have seminiferous atrophy and azoospermia [18].

Another major observation is the occurrence of haematological malignancies in mediastinal germ-cell tumours. A recent review of the literature found 30 cases of associated haemopathies with karyotypic documentation [8]: an i(12p) was observed in 10 cases, a trisomy 8 in 10 cases and a chromosomal marker in 5 cases. Haematological malignancies associated with mediastinal germ-cell tumours occur in young patients, less than 2 years after the mediastinal tumour. The median survival is short (one month) and the phenotypic profile is infrequent (megakaryocytic acute leukaemia, malignant histiocytosis, erythroleukaemia) [19]. There are arguments to postulate that haematological malignancies originate from the pluripotent germ-cells of the germinal tumours. The presence of CD34+ cells within the mediastinal germ-cell tumours has been recently demonstrated [20]. Expression of the p53 suppressor gene protein is frequent in germ-cell malignancies and rare in leukaemias, but it was demonstrated in 3/6 haematological malignancies associated with mediastinal germ-cell tumour [20].

The presence in 30% of the reported cases of leukaemias of an i(12p) is in favour of the germ-cell origin of the haematological malignancy. The clonal origin of this karyotypic abnormality has been demonstrated [21, 22]. No other case of haematological malignancy with an i(12p) has been reported [22]. Finally, there are common cellular-markers in immunochemistry studies in both diseases: germ-cells are able to express antigens CALLA [23] and CD30 [24], conversely leukaemia cells may express germ-cell markers such as cytokeratins [22]. The exact frequence of haematological malignancies in mediastinal germ-cell tumours is unknown: 17 cases in 78 patients (22%) were found in three series [6, 8, 25]. However, this knowledge may help in treatment decisions.

The most important facts we pointed out are: What is the optimal chemotherapy regimen to be given in mediastinal germ-cell tumours? What is the role of surgical exeresis of residual disease? Which salvage treatment should be used? What is the incidence of associated haematological malignancies and, if frequent, what are the treatment options?

The paper by Bower and associates [2] helps to answer to some of these questions. International cooperation is required to study these tumours due to their rarity. In such a study, biopsy specimens of tumours may be used for karyotypic analysis or cryopreserved for molecular studies. A comparison of the BEP regimen versus POMB/ACE regimen could certainly be exciting. A careful study of surgical procedures and specimens is warranted. Follow-up studies may focus on the occurrance of haematological malignancies and their characteristics. Such an international effort could take place in the follow-up of the international study of prognostic factors.

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