Impact of non-pulmonary visceral metastases in the prognosis and practice of metastatic testicular germ cell tumors

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Abstract

Non-pulmonary visceral metastases, in bones, brain and liver, represent nearly the 10% of metastatic sites of advanced germ cell tumors and are associated with poor prognosis. This review article summarizes major evidences on the impact of different visceral sites on the prognosis, treatment and clinical outcome of patients with germ cell tumors. The clinic-biological mechanisms by which these metastatic sites are associated with poor clinical outcome remain unclear. The multimodality treatment showed a potential better survival, in particular in patients with relapsed disease. Patients with advanced germ cell tumors with visceral metastases should be referred to centers with high expertise in the clinical management of such disease.

Introduction

Testicular germ cell tumors (GCTs) are curable solid tumors thanks to the remarkable high chemosensitivity to platinum agents. There is a complex balance between the load of treatment, often concerning on platinum-based chemotherapy and the cure rate in GCT patients, because inappropriate systemic treatment can result in a low rate of cure, whereas the overtreatment may lead to acute and late adverse events. The proper staging of early and advanced disease can provide a more tailored approach to have an optimal treatment burden.

Different factors can contribute to the prognosis of advanced GCT, including the primary and metastatic visceral sites, the type of histology (non-seminoma vs seminoma) and the volume of disease expressed by the level of tumor markers: α-fetoprotein (AFP), β-human chorionic gonadotropin (βhCG) and lactate dehydrogenase (LDH). In particular, primary mediastinal nonseminoma is characterized by a worse prognosis independently from other factors with resistance to standard-dose and high-dose chemotherapy in first-line setting and in relapsed patients. To date, the prognostic impact of visceral disease is well known, but it includes only brain, bone or liver metastases, while pulmonary localization in GCT patients does not belong to the definition of visceral metastases. It is well established that patients with non-pulmonary visceral metastases have a poor prognosis; even recently larger retrospective analyses evaluated the impact of different metastatic sites on prognosis and treatment showing consistent differences within the different groups of metastatic visceral sites. This review article summarizes recent evidences on the impact of visceral disease in the prognosis of patients with advanced GCT.

Prognostic models

In advanced GCT patients, in first-line setting, the prognosis is determined by the International Germ Cell Cancer Collaborative Group (IGCCCG) classification. In this score system prognosis is associated with the presence or absence of nonpulmonary visceral metastases and, for nonseminomatous GCTs only, with the site of the primary tumor (testicular or retroperitoneal versus mediastinal) and with the levels of the serum tumor markers (Figure 1). In this staging score system, the number and diameter of the metastases had not a significant impact on multivariable analysis, whereas prognosis was predicted by the presence of metastases to sites other than the lungs and, for nonseminoma only, by the primary tumor site and the serum level of AFP, βhCG and LDH. Based upon these factors, the IGCCCG classification subdivided GCT patients into good, intermediate, and poor prognosis groups. In this large retrospective analysis, the GCT patients received first-line cisplatin-based chemotherapy between 1975 and 1990; so several results were obtained in particular in the poor prognosis settings, treated with old regimens without the modern dose intensification. A recent meta-analysis has evaluated the prognosis in nearly 1800 patients with nonseminomatous GCT treated with first-line chemotherapy from 1983 to 2002. It reported that five-year survival rate for the good- and intermediate-prognosis subsets were similar to those included in the IGCCCG study, but a 5-year overall survival rate of 71% versus 48% for poor-risk patients has been shown. A better supportive care, including the use of granulocyte-colony stimulating factors, has allowed the correct dose intensity in poor prognosis patients. Moreover, a better management of post-chemotherapy
Residual masses with ameliorated imaging modalities and a use of referring institutions for surgical resection, have contributed to increase the cure rates of these patients.24-29 Lastly, the improved outcomes in poor prognosis patients are related to the better management of salvage treatments, including the use of multi-cycle high-dose chemotherapy in these patients, despite poor results in other solid tumors and the use of new chemotherapeutic agents.30-39 In patients progressing or relapsing after first-line therapy, a new scoring system has been recently validated.9 According to this scoring system visceral metastases (bone, brain or liver) could influence negatively the prognosis, even if mediastinal primary site remains the worst prognostic factor, in spite of the support of high-dose chemotherapy.5 However, it is necessary to distinguish among different organs of visceral metastases.

Bone metastases

The incidence of bone metastases is rare. In a retrospective series of 300 patients with GCT, bone metastases were found in 3% of cases at initial presentation and in 9% at first relapse.40 Another study of 530 patients with GCTs, reported an incidence of 4% of bone metastases at relapse.41 Larger retrospective series on GCT late relapse (>3 years after treatment) did not show bone metastases, so that bone is not a frequent site in late relapsing patients.42,43 The treatment of epidural spinal cord involvement showed improved survival when treated with chemotherapy only in a series of 29 cases. So the authors recommended platinum-based chemotherapy as the best therapy in patients with chemosensitive GCT presented with spinal cord involvement, whereas salvage chemotherapy and/or radiotherapy is suggested in platinum-resistant GCT.44 Screening for bone metastases in patients with GCT is not generally recommended. A retrospective study of 434 poor prognosis patients treated with high-dose chemotherapy within two clinical trials identified 40 patients (9%) with primary bone metastases, most commonly identified in patients with primary mediastinal tumors, yolk sac tumor histology, and synchronous liver metastases.45-47

A large study retrospectively analyzed prognostic factors and treatment of 114 GCT patients with bone metastases at first relapse,48 derived from a database containing 1594 patients (IPFSG study).9 At relapse, 8 patients (8%) had bone metastases only, 40 (39%) concomitant lesions in the lung, 6 (6%) in the brain, 27 (26%) in the liver and/or 69 (66%) in the lymph nodes. Salvage therapy consisted of standard-dose chemotherapy in 35 cases and high-dose chemotherapy in 69 patients. Overall response rate was 81% after high-dose chemotherapy versus 43% after standard-dose chemotherapy (P<0.001), median progression-free survival was 9 months versus 5 months, respectively (P<0.01), and median overall survival was 18 months versus 13 months, respectively (P=0.078). The metastatic dissemination to bone marrow is very rare in GCT.49 According to these retrospective data, high-dose chemotherapy seems a more appropriate option than conventional-dose chemotherapy for GCT patients in bone metastases.

**Good prognosis**

| Non-seminoma (5-y PFS: 89%, 5-y OS: 92%) | Seminoma (5-y PFS: 82%, 5-y OS: 86%) |
|------------------------------------------|-------------------------------------|
| any primary tumor location and           | any primary tumor location and      |
| no extrapulmonary visceral metastases and| no extrapulmonary visceral metastases and |
| AFP<1000, HCG<5000 and LDH<1.5xN         | Normal AFP, any HCG or LDH          |

**Intermediate prognosis**

| Non-seminoma (5-y PFS: 75%, 5-y OS: 80%) | Seminoma (5-y PFS: 67%, 5-y OS: 72%) |
|------------------------------------------|-------------------------------------|
| gonadal or retroperitoneal primary site and | any primary tumor location |
| no extrapulmonary visceral metastases and | normal AFP, any HCG or LDH |
| AFP<10,000, HCG<50,000 and LDH<10xN     | and extrapulmonary visceral metastases |

**Poor prognosis**

| Non-seminoma (5-y PFS: 41%, 5-y OS: 48%)* | Seminoma No patients |
|------------------------------------------|----------------------|
| mediastinal primary tumor or             | In the 90’s the 5-y OS in poor prognosis patients is raised to 60-65% because of the use of G-CSF and better management20 |
| extrapulmonary visceral metastases or    |                      |
| AFP>10,000, HCG>50,000 and LDH>10xN      |                      |

* In the 90’s the 5-y OS in poor prognosis patients is raised to 60-65% because of the use of G-CSF and better management20.

Figure 1. International Germ Cell Cancer Collaborative Group (IGCCCG) classification. PFS, progression-free survival; OS, overall survival; AFP, α fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; G-CSF, granulocyte-colony stimulating factors.
However, there is an urgent need to analyze a major number of GCT patients to determine the best chemotherapeutic approach. In the analysis of IGCCCG classification, bone metastases from pure seminoma are not associated with a poorer prognosis, but this data needs to be confirmed in larger series. To date, the data on bone metastases from GCT derived only from retrospective cohorts of 30-40 cases and from the IPPSG study data on 114 patients. Recently, the Global Germ cell Cancer Group (G3), a consortium of GCT experts, has made a large international retrospective analysis aimed to identify the presence of significant factors related to prognosis and clinical outcome of these patients. The publication of these data is warranted to improve the knowledge of bone metastases from GCT.

**Brain metastases**

Approximately 2% to 3% of patients with advanced GCT develop brain metastases during their clinical history. Several small retrospective studies demonstrated a poor prognosis of these patients, but no further information was provided on clinical features or on the outcome or on the optimal management of these patients, even if multimodality treatment was considered as a treatment of choice in most of these series. The international consortium G3 collected data on 523 fully assessable patients with GCT and brain metastases at first diagnosis (n=228) or at relapse (n=295). In this analysis, brain metastases were associated with nonseminomatous GCT, with a high tumor burden, in particular pulmonary, liver or bone secondary localization, and with high HCG serum levels. The presence of brain metastases is more frequently related to higher tumor burden; however, it has been suggested that patients with brain metastases at initial diagnosis tend to present a better prognosis than previously treated patients. In the latter group, at the multivariate analysis, high-dose chemotherapy and multimodality treatment were the only factor associated with a better outcome.

The negative impact of brain metastases in prognosis of GCT depends also on the addition of other risk factors. High-dose chemotherapy and multimodality treatment could prolong the survival of these patients.

**Liver metastases**

The liver represents the most common non-pulmonary visceral site in most of retrospective series in GCT with nearly 5-6% of cases presenting with visceral metastases at initial diagnosis. According to IGCCCG staging system and the evidences from other major retrospective series, patients with liver metastases could be classified as poor risk patients at initial presentation, representing about 20-25% of patients within the poor-risk group. Consequently, the poor prognosis associated with liver metastatic disease is related to an aggressive GCT and/or late diagnosis rather than a characteristic of liver involvement itself. Hepatic function alterations had no consequences and there were not even symptomatic complications of liver involvement for the management of these patients in terms of risks and benefits. GCT patients with liver metastases should be treated as a poor prognostic category at diagnosis and at relapse.

The impact of the resection of residual hepatic masses from nonseminomatous GCT after systemic therapy has been documented in most cases. Even, retrospective data do not support the routine resection of all residual hepatic metastases persisting after initial approach to metastatic nonseminomatous GCT. Some authors recommended that hepatic resection should be indicated only for patients with residual liver masses from nonseminomatous GCT of more than 1 cm in diameter, when treatable. Anecdotal case reports are available on locoregional approaches, as internal radiation with yttrium-90 microspheres in the treatment of liver metastases.

**Conclusions**

The incidence of visceral metastases is very low in patients with advanced GCT, but it is essential to consider them for the management of these patients, because they represent important prognostic factors. The biological mechanisms by which non-pulmonary visceral metastases are associated with a poor clinical outcome of GCT patients is not completely clear. Different hypotheses could be considered, including a poor penetration of chemotherapy due to specific microenvironment protection of tumor cells, inaccessibility to surgical resection of residual masses after chemotherapy and the fact that these metastatic sites are expression of a specific aggressive biology of these malignancies.

In the present review article, we have summarized data about the impact of visceral metastases from GCT mainly derived from retrospective series, with all limitations of this kind of analysis as selection and reporting prejudice, missing data, as well as different therapeutic approaches and regimens; nevertheless, prognostic factors and supports for decision making in different clinical settings have been presented and should be accounted. A multidisciplinary team for integrated approach including chemotherapy, high-dose chemotherapy, surgical approach, and radiotherapy may prolong the survival and reduce the costs and toxicity related to not appropriate treatments. Thus, patients with advanced GCT with visceral metastases should be referred to centers with high expertise in the clinical management of such disease.

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