Current treatment of high risk testis cancer

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Introduction

The incidence of testicular cancer in Europe is doubling every 20 years. The incidence in Europe is 6.3/100,000/year with the highest rate in North European countries (6.8/100,000/year). Today, cure rates of 95–99% for patients with early stage testicular cancer are achievable, but the prognosis of patients with non-pulmonary visceral disease and/or highly raised tumour markers is generally poor: these patients have a 50% chance of cure.

Patients' prognoses are assessed according to the International Germ Cell Cancer Consensus Conference (IGCCCG) scale, in which patients are assigned to a good (90% seminoma, 56% non seminoma; 90% survival), intermediate (10% seminoma, 28% non seminoma; 80% survival), or poor (16% non seminoma; 60% survival) prognosis group. The assignment of a prognostic group is important to decide the best treatment approach. Serum tumour markers are critical in the assignment of prognosis and management during treatment as well. Serum concentration of alpha fetoprotein (AFP) and/or human chorionic gonadotropin (hCG) are elevated in 80% of patients with advanced non seminoma, and nearly all patients with intermediate or poor-prognosis disease. In seminoma, Laktatdehydrogenase (LDH) and hCG are important markers, but only non-pulmonary visceral metastases separate an intermediate from a good prognosis.

This educational will focus on the treatment of patients with advanced disease which includes intermediate and poor prognosis first-line treatment, salvage therapy and the role of high dose chemotherapy (HDCT).

First-line treatment of advanced germ cell tumour (clinical stage (CS) IS/IIC/III)

Patients in the good prognosis group receive cisplatin, etoposide, bleomycin (PEB) × three cycles, alternatively Cisplatin, etoposide (PE) × four cycles, in particular if bleomycin is contraindicated. PEB can be given in a 3 day or 5 day schedule [1, 2]. In intermediate and poor prognosis patients, PEB × four cycles q d 22 is standard but only as a 5 day schedule. Bleomycin can be substituted by ifosfamide (Cisplatin, etoposide, ifosfamide (PEI)/Etoposide/Ifosfamid/Cisplatin (VIP)).

75% of patients with intermediate-prognosis and 50–60% with poor prognosis achieve a durable Complete remission (CR) with PEB +/– surgery; therefore, development of more active regimens is a priority for these patients. Attempts for improvement have focused on intensifying the PEB regimen, including increasing the cisplatin dose, substituting ifosfamide for bleomycin and using PEB alternating with a second combination regimen. These studies failed to demonstrate any advantage over standard PEB. The randomised study from the EORTC investigating the additional role of paclitaxel to standard PEB was closed transiently due to inadequate recruitment.

Role of high dose chemotherapy (HDCT) in first line therapy

A number of pilot trials have tested the role of HDCT with stem cell support in the first-line treatment of poor risk germ cell tumours (GCTs). Although improved response rates and survival have been suggested, compared to historical controls, a recent small randomised phase III trial ($n = 219$) comparing PEB × four with two cycles of PEB followed by two cycles of high dose carboplatin/etoposide/cyclophosphamide HDCT in intermediate/poor prognosis patients has not shown any advantage (overall survival [OS] 72% for BEP versus 71% for HDCT) [3]. However, in a subgroup analysis, patients who showed a poor marker decline might have benefited from the addition of HDCT. The randomised EORTC trial (30974) explored the evidence from German studies that showed beneficial results for sequential HDCT with one cycle of VIP followed by three cycles of high dose VIP and stem cell support. This trial was closed prematurely due to inadequate recruitment [4]. First results are expected at the end of 2009.

Salvage chemotherapy

Most patients with testicular cancer who achieve a complete response by chemotherapy or chemotherapy + surgery of mature teratoma or necrosis to initial therapy are cured, with relapses occurring in less than 10% of cases. Patients who relapse after initial treatment can still potentially be cured with second-line and even third-line chemotherapy. Both conventional and HDCT play a role in the salvage setting. Prognostic factors, using the Memorial-Sloan Kettering Cancer Center (MSKCC)-score and more recently the scores identified by Lorch and colleagues [5], can identify those patients who are most likely to benefit from conventional dose salvage chemotherapy, sparing them the toxicity of HDCT. However, it is unclear whether patients of any risk group might have benefited from high dose salvage chemotherapy. Prior favourable response (CR/PR–) to first-line treatment and primary retroperitoneal/gonadal primary site are the key prognostic criteria associated with a good chance of achieving a durable CR with standard dose salvage chemotherapy.

Standard first-line salvage chemotherapy for seminoma and non seminoma is four cycles standard dose VIP/Paclitaxel, ifosfamide, cisplatin (TIP)/vinblastine + ifosfamide + cisplatin (VeIP). Relapse after a longer (>3 months) period after initial favourable response does not necessarily represent a platinum resistant situation. Therefore, in this situation, cisplatin is part of salvage treatment protocols, including further agents which have not been used in the first-line treatment. Surgery must be part of the strategy (see below), in particular in those patients with localised or late relapse, who are poor responders to chemotherapy (often yolk sac tumour, alpha-fetoproteine-positive, slow growing teratoma).

In refractory patients, e.g. those who never reached a marker negative CR under first-line treatment or have no favourable response or relapse after salvage treatment, no current standard treatment, can be recommended. Presently, the combination of gemcitabine/paclitaxel seems to be the most appropriate palliative approach out of clinical trials.

Salvage chemotherapy (using either standard or HDCT regimens) for mediastinal non seminomatous germ cell tumours has not been that effective, with a long-term disease-free survival ranging from 0 to 11% including some long term survivors after HDCT (see below).

Second salvage chemotherapy after failure of second-line chemotherapy

All drugs which have not been used in the first- and second-line treatments can and should be used for third-line treatment including the combination of paclitaxel/gemcitabine. Cisplatin can be reinstituted if the tumour is not definitively cisplatin-refractory. In third-line, experimental HDCT is a definitive option, preferably within clinical trials.

As single agents, only orally administered etoposide, paclitaxel, gemcitabine and oxaliplatin have been shown to induce partial responses in 10–30% of patients. However, combinations should be preferred e.g. gemcitabine/paclitaxel. Capecitabine as single agent and irinotecan based chemotherapy demonstrated no activity in phase II trials of patients with cisplatin-refractory or relapsed germ cell tumours.

Role of high dose chemotherapy in salvage therapy

The role of high dose chemotherapy for first- and second-line salvage therapy is rather unclear.

In the European trial (IT-94), 280 patients who experienced relapse after favourable response with progressive disease at least 1 month after completing primary chemotherapy were randomly assigned to four cycles of VIP/VeIP, or three cycles of VIP/VeIP followed by one cycle of high-dose carboplatin, etoposide, and cyclophosphamide (CEC) [6]. This approach failed to significantly improve the 3-year event-free survival rate (42% versus 35% with four cycles of VIP/VeIP) or overall survival (53% in each arm). Of note, the toxic death rate was higher in the HDT arm (7% versus 3%). However, in a large multiinstitutinal series, 63% of 184 patients achieved a durable complete response to high dose chemotherapy with a median follow up of 4 years [7]. Einhorn and colleagues concluded that in patients with relapsed or refractory metastatic testicular cancer, high dose chemotherapy can potentially cure patients, even in those with platinum-refractory disease.

Role of salvage surgical resection

Patients with residual radiologic disease but marker-negative remission following salvage therapy need surgical resection as an integral part of therapy. Surgical salvage is attempted if patients have completely resectable disease and chemorefractory disease (tumour marker progression occurring after salvage

chemotherapy with the lack of chemotherapeutic options or tumour markers failure to normalise). Resection of disease with tumour marker progression despite salvage chemotherapy is termed "desperation surgery". However, only a few selected patients are suitable for complete resection in resistant disease.

Management of late relapses

Most relapses occur within the first 2 years after completion of treatment; those occurring thereafter are termed late relapses, with an estimated incidence of 2–6%. In most reports, the majority of relapses occur more than 5 years after the end of treatment. Late relapses are associated with increased chemotherapy resistance (often yolk sac tumour, alpha-fetoprotein-positive, slow growing teratoma) compared with early relapse and initial disease. Surgery is the mainstay of management and, if technically feasible, radical surgical resection of all lesions irrespective of the level of tumour markers should be attempted. When primary chemotherapy is applied, paclitaxel-containing regimens are recommended, followed by resection of residual disease.

Conclusion

The basis of treatment for advanced testis cancer is chemotherapy and surgical resection of residual disease. Selection of chemotherapy is based on the prognostic assignment. The risk of long term toxicity must be minimised by careful tailoring of the patient's treatment of their prognostic factors. Some patients who are refractory to initial chemotherapy can still be cured with second- or third-line treatment, which includes either ifosfamide-containing regimens or high dose chemotherapy with autologous stem cell transplantation. Novel molecular targets such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors are under investigation and might play a role in the near future.

Conflict of interest statement

No conflict of interest to declare.

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