Management of large volume seminoma, single institution experience

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Background: Advanced Seminoma is a rare clinicopathologic entity. Large volume Seminoma includes patients with Stage II**C-D**, III**C-D**, and IV disease. The objective of this study is to evaluate the efficacy of first-line Etoposide and Cisplatin ± Bleomycin (PE/PEB) chemotherapy in large volume seminoma.

Materials and Methods: Between September 2007 and April 2012 the records of 10 patients were reviewed at King Fahd Specialist Hospital-Dammam, Saudi Arabia. Data extracted included age, date of diagnosis, histopathology, baseline tumor markers (ßHCG, LDH), primary site, baseline clinical stage, baseline risk stratification, first line chemotherapy regimen, number of cycles, type of toxicity, overall response, date of relapse, second line treatment and current status.

Results: Median age at diagnosis was 32 years with a range of (17-49). Median follow up was 32 months (range 4-54). The primary site of disease was gonadal in 8 patients, 3 of them with undescended testis (stages IID, IIC, and IIB) and the remaining 5 patients with stages IIB, IIB, IIC, IID, and IVC, L1. Primary mediastinal affection was seen in 2 patients with stages IIIC and IIID. Nine patients had classical seminoma, 1 patient had spermatocytic seminoma. Baseline serum BHCG was high in 4 patients and baseline serum LDH was high in 4 patients as well. All patients had good risk according to IGCCCG. All patients achieved complete response after first line PEB / PE chemotherapy. Two patients with primary mediastinal disease received consolidation mediastinal irradiation, 1 patient with undescended testis received para-aortic nodal irradiation. One patient (8.3%) relapsed in the mediastinum and retroperitoneal lymph nodes and was salvaged with second line chemotherapy and para-aortic nodal irradiation. At the last follow-up evaluation, all patients are alive and disease-free.

Conclusions: Regardless of histological subtype, the presence or absence of adverse prognostic factors, seminoma treated with PE/PEB regimen showed a favorable response to first-line chemotherapy, and achieved an excellent outcome. Even large volume disease is exquisitely sensitive to three cycles of BEP, eliminating the need for dual or subsequent therapy. Elevations of the serum HCG, LDH were not associated with an adverse prognosis.

Introduction

Testicular tumours accounts for about 1% of all male malignancies and are in 95% of cases of germ cell origin (1). Seminoma constitutes approximately 50% of all germ cell tumours and is increasing in incidence. The peak incidence occurs between thirty and forty years of age (2).

For treatment purposes, two broad categories are recognized: pure seminoma, and all others, which together are termed nonseminomatous germ-cell tumors (NSGCT). Seminoma, 80% of which are diagnosed at stage I, is highly sensitive to both radiotherapy and chemotherapy and, therefore, unlike many malignant neoplasms, cure is an expected outcome in the majority of cases, even with metastatic disease at presentation. Its prognosis is generally good, but the treatment-induced morbidity must not be underestimated (3).

For higher stages of seminoma there is international consensus on treatment with multiple courses of cisplatinum based combination chemotherapy (4, 5). As patients with advanced seminoma are infrequent there are no randomized studies comparing different kinds of cisplatinum-based chemotherapy. However, these patients were often included in protocols for low risk testicular cancer irrespective of histology. Results from these studies have shown that 4 cycles of EP (Etoposide and Cisplatinum) are as effective as other cisplatinum regimens (6). No studies support the use of single agent carboplatin chemotherapy in advanced disease (7, 8). According to the Modified after the Royal Marsden Hospital staging system; large volume disease is clinical stage (CS) IIC-D, IIIC-D, IVC-D, L1-L2 and very large volume disease is CS IV0-D, L3-L4; extralymphatic extrapulmonary metastases (bone, liver, brain), **table1** (9).

Materials and Methods

During the period between September 2007 and April 2012 the records of 10 patients with large volume seminoma were retrospectively reviewed. Data extracted included age, date of diagnosis, histopathology, baseline tumor markers (ßHCG, LDH), primary site, baseline clinical stage, baseline risk stratification, first line chemotherapy regimen, number of cycles, type of toxicity, overall response, date of relapse, second line treatment and current status. Tumors were staged according to the Modified after the Royal Marsden Hospital staging system and patients were stratified according to the International Germ Cell Collaborative Consensus Classification Group (IGCCCCG), **table 2 and 3.**

Results

Table 4 provides a summary of patient characteristics such as age, stage, treatment, follow-up, and overall survival. Total of 10 patients were reviewed. Median age at diagnosis was 32 years (17-49). Median follow up was 32 months (4-54). Baseline staging work up included CT chest, abdomen and pelvis in 9 patients and the remaining 1 had both CT and PET-CT as baseline imaging work up. The primary site of disease was testicular in 8 patients, 3 of them diagnosed with undescended testis with clinical stages IIB, IIC, and IID, and the remaining 5 patients with clinical stages IIB, IIB, IIC, IID, and IVC, L1. Primary mediastinal in 2 patients with clinical stages IIIC and IIID. Nine patients had classical seminoma and 1 patient had spermatocytic seminoma. Baseline serum BHCG was high in 3 patients and baseline serum LDH was high in 3 patients as well. All patients were good risk according to IGCCCG.

Nine patients treated with PEB (Cisplatin, Etoposide and Bleomycin) regimen, 5 patients received 4 cycles of PEB and 4 patients treated with 3 cycles. One patient treated with 3 cycles of EP (Etoposide and Cisplatin) regimen without Bleomycin due to lung pathology. All patients achieved complete response.

Two patients with primary mediastinal disease received consolidation mediastinal irradiation with a total radiation dose of 3600 cGrey, 1 patient with undescended testis received para-aortic nodal irradiation.

One patient relapsed in the mediastinum and retroperitoneal lymph nodes on follow up PET-CT and was salvaged with second line chemotherapy, in the form of 2 cycles of VIP (Vinblastine, Ifosfamide and Cisplatin) regimen followed by para-aortic nodal irradiation.

All patients completed their planned cycles of chemotherapy. Seven patients had no major toxicities, 3 patients had febrile neutropenia and needed admission into the hospital and 1 patient had ototoxicity in the form of tinnitus. One patient had grade IV hematologic toxicity with the second line chemotherapy regimen. . At the last follow-up evaluation, all patients are alive and disease-free.

Discussion

Testicular cancers, 95% of which are germ-cell tumors (GCT), are the most common solid malignancies affecting males between the ages of 15 and 35 years, although it accounts for only about 1% of all cancers in men. In 2010 it caused an estimated 350 deaths with 8480 new cases diagnosed in the United States alone (10). Its prevalence is one of the world's highest, and is still increasing (11). Nevertheless its origin remains poorly understood, although some environmental or genetic risk factors are suspected (3). Little is known about etiological risk factors for the development of testicular tumours. Ten percent of the patients have had a history of cryptorchidism. Some epidemiological studies show a significantly increased percentage of pure seminoma as compared to germ cell tumours of other histologies in men with undescended testis (12). Other risk factors are hypotrophic testicle and infertility (13).

Most of the studies on advanced germinal cancer include both seminoma and nonseminomatous tumors (14). As there is no bad prognostic subtype for advanced pure seminomas, most of the centers tend to treat them in the same way as the bad prognostic subtypes of nonseminoma. The current standard treatment consists of 3-4 cycles of BEP or EP chemotherapy regimens (15). There are no randomized studies on patients with stage IIB disease comparing radiotherapy and chemotherapy. The reported relapse rate with radiotherapy varies between 9–24%. All available data are based on small series of patients. The relapses after radiotherapy are predominately located outside the retroperitoneum. Even if the risk factors for subclinical disseminated disease in stage IIB disease are unknown it is reasonable to believe that tumour volume is of importance. Both radiotherapy and chemotherapy are viable alternatives (16). For higher stages of seminoma there is international consensus on treatment with multiple courses of cisplatinum based combination chemotherapy (5). In the International Germ Cell Consensus Classification **(table3),** a prognostic factor-based classification system for metastatic germ cell cancers, metastatic seminoma is classified as good or intermediate prognosis. No seminoma patients are classified as poor risk. Adverse prognostic factors are non-pulmonary visceral metastases, especially liver or brain. Also, presence of supra clavicular nodes and raised LDH (>two times the upper limit of normal) added negative prognostic information (17).

Seminomatous tumours are often characterized by slow clinical regression rate following chemotherapy. Residual tumour mostly consists of fibrotic or necrotic tissue. In post-chemotherapy seminoma residuals, a positive PET is highly predictive for the presence of viable tumour especially when using a ≥3 cm cut-off. A negative PET scan is excellent for the exclusion of disease in lesions ≥ 3 cm. PET can contribute to the management of residual seminoma lesions, especially in terms of avoiding unnecessary additional treatment for patients with non-regressing lesions ≥ 3 cm (18).

By the late 1980s, investigators realized that certain clinical and tumor features could predict the likelihood of patient response to standard chemotherapy regimens. Several algorithms were developed to stratify patients into "good" or "poor" prognostic groups and were incorporated into clinical trials in order to test treatment strategies in specific patient populations. Differences between the algorithms made it difficult to compare trial results. The International Germ Cell Cancer Collaborative Group (IGCCCG) was formed, and a universal classification scheme was developed.2 In this stratification system, patients are separated into good-, intermediate-, and poor-prognostic groups according to predicted outcome to cisplatin-combination chemotherapy, based on histology, primary site, sites of metastasis, and serum tumor marker elevation (19).

Seminoma can be divided into three pathologic categories: classical, spermatocytic, and seminoma with syncytiocytotrophoblastic cells. The spermatocytic type is rare, occurs in older men, and may have a better prognosis. The classical and the syncytiocytotrophoblastic types of seminoma behave similarly, although the syncytiocytotrophoblastic subtype is associated with increased serum ß-HCG levels. Occasionally, seminoma may contain numerous mitotic figures. When three or more mitotic figures are identified per high power field throughout the tumor, it is designated as seminoma with high mitotic index or anaplastic seminoma (20).

Cisplatin dose-intensified chemotherapy does not seem to be superior to standard BEP or radiotherapy (21). Post therapeutic follow-up modalities consist of a four-week post chemotherapy thoraco-abdomino-pelvic CT scan (22). The subsequent management depends on the size of the residual mass. If the latter is less than 3 cm in diameter, a simple surveillance in advised. If it is larger, a PET-CT exam is recommended. If the latter remains positive, a definitive confirmation by biopsy is necessary. If the PET-CT is negative, surveillance may be sufficient (23). In the presence of active residual tumoral tissue, radiotherapy or chemotherapy remains the treatment of choice (23).

In the case of relapse after chemotherapy, and if it occurs less than three months after one chemotherapy cycle, the disease is still considered to be sensitive to a platinum-based chemotherapy salvage treatment (24). The chemosensitivity persists even after the second or third chemotherapy cycles. Cisplatin is the fundamental drug that must be part of any salvage chemotherapy (25). The most used first line salvage protocols are the VIP (cisplatin, etoposide, and ifosfamide), TIP (paclitaxel, ifosfamide, cisplatin) or VeIP (vinblastine, ifosfamide, cisplatin) schedules. In fact, relapse after a platinum-based chemotherapy is very rare, and about 50% of them are cured by salvage chemotherapy (26).

Conclusion

Seminomatous germ cell tumors treated with cisplatin based chemotherapy (PE/PEB) regimens showed a favorable response to first-line chemotherapy, and achieved an excellent outcome. Even large volume and very large volume diseases is exquisitely sensitive to standard chemotherapy; some patients who relapse after initial chemotherapy can still be cured with second-line salvage therapy eliminating the need for dual or subsequent therapy.

Tables

Table 1: the Modified after the Royal Marsden Hospital staging system developed by Peckham 1981

Clinical Stage	Definition
CS I	No evidence of metastasis.
CS Mk	β-HCG persistently elevated (not declining according to its half-time), but no metastatic disease demonstrated.
CS II **CS IIA** **CS IIB** **CS IIC** **CS IID**	Metastatic disease is limited to abdominal lymph nodes. Maximal transverse diameter is less than 2 cm Maximal transverse diameter is less than from 2 to 5 cm Maximal transverse diameter is less than 2 cm Maximal transverse diameter is less than 2 cm
CS III	Supradiaphragmatic node involvement
CS IV **Lung substages:** **L1** **L2** **L3** **L4** **H+** **Br+** **Bo+**	Extra-lymphatic metastasis ≤ 3 metastases, no metastases >2 cm > 3 – ≤ 20 metastases, no metastases >2 cm ≤ 20 metastases, > 2 cm >20 metastases Liver metastases Brain metastases Bone metastases

Table 2: Medical Research Council groupings

Group	Definition
Small volume disease	CS Mk+, IIA-B, III0-A-B, L1-2
Large volume disease	CS IIC-D, IIIC-D, IVC-D, L1-L2
Very large volume disease	CS IV0-D, L3-L4; extralymphatic extrapulmonal metastases (Bone, liver, brain)

Table 3: International Germ Cell Collaborative Consensus Classification

Prognostic risk groups	Seminoma	Non-seminoma
Good Prognosis group	90% of seminomas All of the following criteria: Any primary site No non-pulmonary visceral metastases Normal AFP Any ß-HCG Any LDH 5-year survival 86%	56% of non-seminomas All of the following criteria: Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP <1,000 µg/L ß-HCG <5,000 IU/L LDH <1.5 x *n* 5-year survival 92%
Intermediate prognosis group	10% of seminomas Any of the following criteria: Any primary site Non-pulmonary visceral metastases Normal AFP Any ß-HCG Any LDH 5-year survival 72%	28% of non-seminomas All of the following criteria: Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP >1,000 and <10,000 µg/L or ß -HCG >5,000 and <50,000 IU/L or LDH >1.5 and <10 x *n* 5-year survival 80%
Poor prognosis group	No patients classified as poor prognosis	16% of non-seminomas Any of the following criteria: Mediastinal primary Non-pulmonary visceral metastases AFP >10,000 µg/L or ß-HCG >50,000 IU/L or LDH >10 x *n* 5-year survival 48%

AFP = alpha-fetoprotein; ß-HCG = beta-human chorionic gonadotropin; LDH = lactate dehydrogenase.

Table 4: Patients' characteristics

Patients' characteristics	Number of patients
Age in years: Median Range	 32 17-49
Clinical stage: CS IIB CS IIC CS IID CS IIIA CS IIIC CS IIID CS IVC,L1	 3 2 2 0 1 1 1
Undescended testis	3
Primary mediastinal disease	2
Primary testicular disease	8
PEB regimens: 4 cycles 3 cycles	 5 4

EP regimen	1
Number of relapses	1
Second line chemotherapy	1
Salvage radiotherapy	1

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