CURRENT VIEWS IN THE TREATMENT OF NONSEMINOMATOUS GERM CELL TESTICULAR TUMORS AND POLICY IN MARMARA UNIVERSITY HOSPITAL

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Testicular cancer still has the highest incidence among the cancers of 15 to 34 years old age group (1), but fortunately recent advances in the diagnosis and management of the disease have increased its potential curability.

With modern multimodality therapy (chemotherapy, radiotherapy, and surgery) all patients with testicular neoplasms regardless of their stage, are potentially curable (2). Drammatic improvements especially reevaluation of traditional treatment modalities in the chemotherapy for the disseminated disease, reguired the reevalution of traditional treatment modalities(3 - 8).

Testicular cancer can be divided into several histologic types, but classification into pure seminomatous and nonseminomatous germ cell tumors (NSGCT) is the most important clinical distinction (9), in relation to tumor behaviour and response to treatment modalities. As an example, radiotherapy is the treatment of choice for localized seminoma with a cure rate of 90 - 95% (10), where NSGCT are managed primarily by surgery and/or Cis-platin based combination chemotherapy (11).

Until recently management of stage I NSGCT involved radical or modified retroperitoneal lymph node dissection (RPLND) after orchiectomy and surveillance afterwards. But since the 10 % or so who relapse as stage II or III after RPLND on clinical follow-up will be rescued by effective combination chemotherapy, the attitude in the management of proven stage I disease may become more conservative with a close follow-up after orchiectomy.

Although excellent treatment results have been reported with radical node dissection without chemotherapy (12), or with radical node dissection and routine chemotherapy (13), and radiotherapy (14), historical data (15) strongly suggests that at least 80 % of men with clinical stage I disease are likely to be cured with orchiectomy alone and nearly all patients can be rendered disease free following chemotherapy at relapse.

The issue under investigation is obtaining curability with avoidance of unnecessary therapy. In a prospective study Peckham et al (16) showed that, only a minor group of patients have relapsed during surveillance, with the highest incidence in embryonal carcinoma (46 % of this group relapsed), where a low incidence of occult metastases were found in teratocarcinoma.

Related to the relapses, two factors with prognostic significance were identified: The behaviour of serum markers following orchiectomy and involvement of the spermatic cord by the tumor (17). Histology of the tumor may be another factor, although diverse conclusions can be drawn from the literature (16). Under the light of current investigations, orchiectomy alone can be the choice of treatment in proven stage I disease with application of combination chemotherapy when relapses occur.

Results reported so far show a steady improvement in the survival for stage II patients as stage I NSGCT, with either radiotherapy or node dissection (18, 19, 20), having better results in the latter method (90 % versus 94 %) (21).

Patients with metastatic disease are generally subdivided into two categories: small volume and large volume metastatic disease. There is a significant difference between the survival characteristics of these two groups. In patients with small volume metastases a survival rate of 100% can be achieved with meticulous RPLND, including a close follow-up and combined chemotherapy in case of relapses (22).

Similar results were reported with adjuvant chemotherapy (13, 23) indicating that the risk of relapse after node dissection is high enough - (13- 37 %, mean 20 %) (24) to justify adjuvant chemotherapy, addressing the fact that adjuvant therapy markedly reduces or even eliminates systemic recurrence (13, 23, 25). Though it is noteworthy that approximately 65 % of the patients with stage II disease would not have recurred without chemotherapy and thus have been treated unneceessarily (22), also nearly 100% of patients who are relapsing can be rendered disease free with systemic combination chemotherapy

if relapses were detected early. Finally reports appeared in the literature (26) that patients with prior chemotherapy have significantly worse prognosis than the non-pretreated group. Also those patients receiving adjuvant therapy may be subjected to the risk of infection and sepsis during therapy, myelosupression, a risk of renal damage from Cis-platin which may or may not be reversible, a risk of vascular disease (including Raynoud phenomenon, Lhermitte Syndrome, hypertension, MI), impairment of fine sensation, finger thickening, stiffness, and tenderness, and pulmonary fibrosis due to Bleomycin, and a theoretically risk of later development of secondary malignancies and infertility (24, 26).

The most popular form of treatment policy concerning the advanced disease or high volume metastases was to treat patients with four courses of PVB (3). In 1980 BEP replaced PVB as the first line treatment (24, 27).

Patients were reassessed after four cycles of chemotherapy. If disease was initially bulky or if normalization of serum markers was slow, a further two cycles can be given.

In patients attaining complete remission (CR) (27) monthly evaluation of chest X-rays and serum markers (Beta-HCG, AFP) for one year then bimonthly during the following year should be performed.

Patients with residual masses after chemotherapy should be subjected to surgery. In case of histological evidence of residual malignancy in surgical specimen, chemotherapy is continued.

Patients with proven histological data of fibrosis or necrosis or mature teratoma, providing total excision, are also accepted as CR, with close follo-up afterwards (28).

Although most patients with residual teratoma are in CR, carcinoma which may occur months to years later necessitates complete, careful resection of all the residual masses (29, 30, 31, 32, 33).

With this policy more than 80% of patients with bulky metastases could be rendered disease free.

Our current policy is to treat patients with orchiectomy in stage I and surveillance afterwards. This to be done, results of the whole body computerized tomographic examination, retroperitoneal ultrasonography, and bipedal lymphangiography should reveal no evidence of disease after orchiectomy and tumor marker levels must be negative.

Patients are controlled monthly during the first year and bimonthly in the second year. During the third year they are followed up quarterly and then on twice a year.

In case of relapses during follow up, patients are treated with 4 cycles of Cis-platinum-Vinblastine-Bleomycin (Einhorn or PVB regimen).

In stage II disease, in order to figure out whether there are limited or advanced metastases in paraaortic lymph nodes, we perform bilateral RPLND. It is of utmost importance to show the localization of metastases and whether there is spreading outside the capsule of the nodes. If limited stage II disease is found after RPLND, then surveillance is the choice of policy. If it is revealed as advanced stage II disease then again 4 courses of PVB regimen are given to the patients.

In stage III tumors, if the metastases are low volume, it is our policy to treat these patients with 4 cycles of PVB regimen similar to those ones in stage II disease.

In cases of high volume metastases, the procedure is to treat these patients with 4 cycles of Bleomycin-Etoposide-Cis-platinum (BEP) regimen. We perform RPLND and mass excision if a mass is present after this course of chemotherapy, providing the tumor markers are normalized. Next step is moderated by the results of the pathological examination of the surgical specimen. In case of presence of carcinomatous elements in the excised mass, then 2 courses of further BEP are given to our patients. If there is no evidence of cancer or mature teratoma is revealed in microscopic examination, patients are accepted as achieved complete remission (CR), if the mass is totally excised.

Persistence of tumor with elevated levels of markers after 2 courses of BEP makes Vinblastine -I fosfamide - Cis - platinum (VIP) regimen the treatment of choice, given as 4 cycles.

VIP is also used as the first line treatment in patients with very high volume metastases and poor risk (e. g. lung, liver, CNS metastases, nodes greater than 10 cm., Beta-HCG greater than 50.000 u. or poor risk patients with primary extragonadal tumors).

Following this chemotherapy program, if feasible, surgery is recommended for the total excision of remaining tumor of mass reduction.

With this current policy we have reached a cure rate of 75% in patients with advanced stage NSGCT, in our department (27).

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