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Review paper

Treatment of advanced seminoma: an update

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In this update, the recent developments in the treatment of patients with advanced seminoma are reviewed. Also, the approach for patients with residual disease after chemotherapy is described. It is concluded that the combination of etoposide and cisplatin seems to be the standard treatment for patients with advanced seminoma, showing a durable response in about 90% of the patients. Although the combination of etoposide and carboplatin is less effective, newer carboplatin-based combinations seem to have a comparable efficacy. Residual disease after chemotherapy can be safely observed if the diameter is less than 3 cm; however, residuals larger than 3 cm frequently show a vital tumor and surgical evaluation should therefore be considered.

Key words: Chemotherapy, disseminated, residual disease, seminoma.

Introduction

Testicular germ cell tumors are relatively rare, representing about 1–2% of all male human malignant tumors. However, they are the most common malignancies in young adult men and they have become the showpiece of medical oncology as this group of malignancies represents the most impressive example of medically curable malignancies. These tumors are divided into two main clinicopathological groups: the seminomas and the non-seminomas. About 40–50% of the testicular germ cells are classified as seminomas.[1,2]

Although this diagnosis is routinely associated with the male gender, it should be kept in mind that the counterpart of this tumor in the ovary, in the form of the so-called dysgerminoma, is also exquisitely curable.

In contrast to patients with non-seminomas, who often present with more advanced tumors, 70–80% of the patients with testicular seminoma present with stage I disease and 5–10% has supradiaphragmatic or visceral metastases.[3–5] The treatment of patients with stage I or stage II disease consists of radiotherapy, that can be given in a low dose of 25–35 Gy, to the para-aortic and pelvic lymph nodes.[3,6] In analogy with the policy in low-stage non-seminoma, some centers use a surveillance policy of stage I seminoma.[6] Although radiotherapy is an excellent curative option in patients with limited node involvement, in patients with bulky retroperitoneal lymph node metastases it is accompanied by a high risk of relapse. In these patients with large retroperitoneal abdominal masses, therefore, chemotherapy has become the conventional treatment. In clinical practise, patients with retroperitoneal lymph node metastases, measuring more than 5–10 cm in transverse diameter, and patients with supradiaphragmatic and visceral metastases,[3,6] will nowadays receive chemotherapy as first choice. Recently, a consensus was reached concerning prognostic factors for metastatic germ cell tumors including seminomas, to be treated with cisplatin-based chemotherapy.[7]

Staged according to these guidelines, approximately 90% of the patients with advanced seminoma have good prognostic factors, relating to a 5 year survival of 86%. Approximately 10% have intermediate prognostic factors, including bone, liver and brain metastases. The 5 year survival of the latter group is still 73%.[7] An initially almost incurable group is therefore much more difficult to predict than is the case in non-seminoma.

In this review, an update will be given on the treatment of advanced seminoma.

Treatment

The vast majority of patients with disseminated germ cell tumors, including seminoma, are curable with the currently available combination chemotherapy.

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This observation stands in contrast to the results obtained with chemotherapy in other disseminated malignancies. This difference in response to chemotherapy has been the focus of much attention. One of the obvious candidates for an explanation is the gene that controls many of the possible events after exposure to anticancer treatment, the p53 tumor suppressor gene.

This p53 gene plays a key role in the DNA damage-related apoptosis[8] and mutations in this gene are considered to be related to chemo-resistance.[9] Studies of the p53 gene and protein in human testicular germ cell tumors,[10] in familial and bilateral testicular tumors,[11] and in murine terato carcinoma cell lines[12] have not detected p53 gene mutations. If anything, high levels of normal p53 protein were demonstrated. The presence of the wild-type p53 in these tumors possibly provides the basis for its chemosensitivity. However, although p53 mutation is a common aberration in human cancer it is not ubiquitous, while germ cell cancer stands virtually alone in its curability.

In addition, the response control of p53 is probably not different for chemotherapy and for radiotherapy; nevertheless, the effect of radiotherapy in non-seminoma is much less evident than in seminoma. Therefore, other factors must also contribute to this chemosensitivity, such as the level of topoisomerase II, the target for etoposide, a major drug in this disease,[13] Bcl-2[14] or other molecular genetic abnormalities.[15–17] The intracellular pharmacology, both intra-cytoplasmatically and intranuclearly, of cisplatin may also be different in germ cell cancer.

The major advance in the chemotherapy of disseminated germ cell tumors came with the combination of cisplatin, vinblastine and bleomycin (PVB).[18] In their original article, Einhorn and Donohue described four patients with advanced seminoma and three of these patients achieved a complete remission.[18] Although even before that era actinomycin- and vinblastine-based chemotherapy could be curative in some patients, their results were greeted very much as a 'magic bullet' effect and no randomized trial has ever been considered necessary to prove the effect of this cisplatin-based combination. In consequence, then, cisplatin-based chemotherapy has become the standard treatment. The original combination PVB, although with reduction of the vinblastine dose, has been used in the treatment of advanced seminoma by a number of authors.[19–23] In some studies doxorubicin was added to PVB.[21,23] With these combinations a complete response was achieved in 80–90% of the patients, with a durable complete remission of 70–80%. Since the introduction of etoposide into the chemotherapy regimens for testicular cancer, the combination of cisplatin, etoposide and bleomycin (BEP) has also been applied for advanced seminoma.[23–26] Although randomized trials in advanced seminoma comparing PVB with BEP are not available, the efficacy of BEP seems to be comparable to PVB, as is the case of a regimen using alternating cycles of PVB and BEP,[27] while the toxicity of the BEP combination is less. Based on the efficacy of alkylating agents such as cyclophosphamide or ifosfamide, some authors used the combination of cyclophosphamide with cisplatin,[28] vinblastine, ifosfamide with cisplatin[29] or vincristine, ifosfamide with cisplatin,[30] achieving 87–92% long-term disease-free survival. Probably related to the age of the patients and to previous radiotherapy, these regimens are associated with a high risk of myelotoxicity, for which dose reduction and postponement of therapy are necessary in a high percentage of patients (more than 50%).

Researchers at the Memorial Sloan-Kettering Cancer Center have used VAB regimens, including VAB-6, consisting of cyclophosphamide, vinblastine, dactinomycin, bleomycin and cisplatin, in the treatment of metastatic seminoma.[31,32] After a median follow-up of more than 47 months, 37 out of 45 patients (80%) were alive without disease. Because it was the impression that the majority of previously untreated patients with seminoma had a good prognosis, these patients were included in a randomized trial comparing etoposide plus cisplatin (EP) versus VAB-6.[33] It was concluded that four cycles of etoposide 100 mg/m^2 days 1–5 plus cisplatin 20 mg/m^2 days 1–5, every 3–4 weeks, was an efficacious and less toxic regimen. A recent update showed a durable response with VAB-6 in 34 of 43 patients (79%) and with EP in 55 of 60 patients (92%).[34] Since then, etoposide and cisplatin seems to be the standard therapy for patients with advanced seminoma, especially because the substitution of carboplatin for cisplatin proves to be inferior in these patients.[35]

Because of the toxicity of cisplatin-containing combination chemotherapy, including renal tubular damage, severe nausea, and vomiting and neuro- and ototoxicity, Horwich *et al.* in 1989 analyzed the activity of four to six courses of single-agent carboplatin in patients with advanced seminoma.[36] Thirty-four patients were treated, 27 remained continuously disease free, six patients had progressive disease, but five of them were successfully retreated with cisplatin-containing chemotherapy. An extension of their experience was published in 1992.[37] A total of 70 patients had then been treated. Two

patients died of intercurrent disease while in remission, 52 patients (74%) had a 3 year relapse-free survival after a follow-up of 36 months (range 8–101 months). Sixteen patients relapsed, 12 patients (75%) remained free from further relapse after intensive cisplatin-based combination chemotherapy.

Other centers have also used single-agent carboplatin. Dieckmann *et al.*[38] reported disease-free survival in six out of six patients. Schmoll *et al.*,[39] including the patients of Dieckmann,[38] treated 42 patients. Four patients had disease progression and eight patients relapsed. Out of these 12 patients, eight achieved a complete remission after retreatment with cisplatin-containing regimens, leading to a 71% continuously disease-free survival and a 93% total survival after a median follow-up of 30 months. Although carboplatin as a single agent is less toxic than cisplatin combination chemotherapy, the number of patients who fail and therefore require salvage chemotherapy is too high. Because of this failure rate, single-agent carboplatin cannot be recommended as a first-line treatment in patients with advanced seminoma.[37,39,40]

Carboplatin in combination with etoposide has been evaluated versus cisplatin and etoposide in patients with good-risk germ cell tumors, including seminoma patients.[35] A complete response was observed in 27 of 31 seminoma patients (87%), treated with four cycles of 100 mg/m^2 etoposide and 20 mg/m^2 cisplatin on days 1–5, every 3 weeks, while no relapses occurred. In the group of seminoma patients treated with four cycles of 100 mg/m^2 etoposide on days 1–5 and 500 mg/m^2 carboplatin on day 1 of each cycle, every 4 weeks, 31 of 33 patients (94%) reached a complete remission; however, four patients (13%) relapsed, resulting in a 82% durable complete response.[35] Mencel *et al.*[34] and Puc *et al.*[41] also mentioned the results of the combination carboplatin and etoposide, although a number of their patients have been included in the analysis of Bajorin.[35] Mencel *et al.*[34] obtained a durable complete response in 29 of 35 patients (83%), with a median follow-up of 27.5 months (range 7.7–57.4). Puc *et al.*[41] observed one failure out of 21 patients with advanced seminoma. From these results it can be concluded that the combination carboplatin and etoposide is inferior compared to the combination cisplatin and etoposide in the treatment of advanced seminoma.

Amanto *et al.*[42] treated 43 patients with advanced seminoma with the combination carboplatin 400 mg/m^2 day 1 and ifosfamide 1.5 g/m^2 days 2–5. All patients received a minimum of four cycles at 28 day intervals. The number of evaluable patients was 42, and 30 achieved a complete remission (71%), while in 10 patients a complete response was achieved after chemotherapy plus consolidation consisting of radiation therapy or surgery. The remaining two patients did not respond, but one achieved a complete remission with salvage chemotherapy. Two relapsing patients also achieved a second complete remission with salvage treatment. Overall, 41 patients (98%) were disease-free with a median follow-up of 39 months. Recently, Sleijfer *et al.*[43] published their results, using four cycles of 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine and carboplatin adjusted to creatinine clearance (mean dose 400 mg/m^2, range 300–450 mg/m^2) at intervals of 21 days in 27 patients with advanced seminoma. After a median follow-up of 26 months only one patient relapsed.

It should be stressed that direct controlled randomized studies between these various treatment regimens are not available, this is probably due to the rarity of the disease, as well as to the high cure rate available with most combinations. However, from all these studies, it can be concluded that carboplatin-containing combination chemotherapy is an effective regimen for advanced seminoma, but that it cannot simply be substituted for cisplatin. Although the combination of carboplatin plus etoposide is less effective compared to cisplatin plus etoposide, the combination of carboplatin plus ifosfamide or plus cyclophosphamide and vincristine deserves further evaluation in randomized trials, if such trials were ever to be found feasible to perform.

Residual disease

On completion of the remission-induction chemotherapy for disseminated germ cell tumors, residual tumors are regularly still found when a post-treatment evaluation with CT scanning or MRI is performed. Consequently, most centers recommend surgical resection for patients with radiological residual disease after chemotherapy for non-seminomatous germ cell tumors because of the presence of viable tumor and/or mature teratoma.[44,45] The first finding would probably lead to further treatment, although occasionally surgery alone is curative in such situations. Resection of mature teratoma would prevent growth and development of second malignancies in these lesions. However, the approach for patients with seminomatous germ cell tumors and residual disease after chemotherapy remains controversial. The finding of mature teratoma in the resected specimen is excluded in patients with pure seminoma, and especially resection of retroperito-

neal masses is more difficult and is accompanied by more complications due to the tremendous fibrotic reaction compared to non-seminomatous residual masses.[20,46,47] The reason for this fibrotic reaction is obscure as for both tumors apoptotic cell death, directed by the p53 gene, is considered to be the basis of the chemotherapy effect. This process in the physiological situation does not leave scar tissue, while usually complete remission of other tumors on chemotherapy does not leave rest-lesions.

Based on the studies of Motzer *et al.*[32,48] and on their updated experience in 104 patients,[41] the size of residual disease provides an indication of which masses contain viable tumor. Patients who have normal radiographs or residual disease less than 3 cm after cisplatin-based combination chemotherapy showed site failures in only 3% (two out of 74), compared to 27% (eight out of 30) with residual masses above 3 cm. Although some other authors also found a relationship between the size of the residual mass and relapse,[27] neither Schultz,[26] Horwich[36] nor Fossa[30] could find such a relation. It should be noted that these studies comprise a relatively small sample size compared to those of Puc *et al.*[41] However, all authors seem to agree that observation without surgery or radiation therapy is indicated in patients with a residual mass smaller than 3 cm. For patients with a residual mass larger than 3 cm, close observation can also be justified.[26,30,36,43] Fossa *et al.*[30] recommend observation for up to 1 year after chemotherapy because shrinkage of post-chemotherapy mass is a phenomenon known to occur often in seminoma. Others, however, still prefer surgery to close observation for large residual masses.[41] Surgery gives an immediate assessment of the response and can consist of resection of the mass without a lymph node dissection or of multiple biopsies.[41] In case of viable tumor second-line chemotherapy or irradiation,[41] even intra-operative irradiation,[49] can follow. The last option for patients with large residual disease is irradiation which has been used in some or all eligible patients.[22,24,36,42,50] Irradiation in all patients means that many would be treated unnecessarily and therefore will be exposed to acute and long-term radiation-related toxicity including secondary malignancies.[51] Therefore, an accurate test to predict when a residual mass contains necrotic fibrous tissue or viable carcinoma will be worthwhile.

The use of gallium scans proved to have only minimal value in the evaluation of post-chemotherapy residual mass.[52] The results of studies using positron emission tomography is these circumstances also are disappointing.[53,54]

Salvage therapy

In recent years it has become clear that late relapses, after initially effective therapy, can be retreated with cisplatin-containing chemotherapy in the case of non-seminoma. Probably the same is true for seminoma. Also early relapsing seminoma, although extremely rare, might be considered to be an indication for ablative chemotherapy. For both treatments more toxicity can be expected in these patients than in non-seminoma patients, because of their age and frequent prior treatment with radiotherapy. If in such late or early relapses a reliable localization of tumor can be found, radiotherapy should be considered at least as a palliative option.

Conclusion

The incorporation of cisplatin in polychemotherapy regimens for the treatment of advanced seminoma has dramatically increased the curability of these patients. However, because only a minority of patients with seminoma present with advanced disease, randomized trials comparing different treatment schedules in these patients are lacking. Nearly all advanced seminomas are considered to have good prognostic factors and therefore are included in randomized trials for good prognosis germ cell carcinomas, including a majority of non-seminomas. Based on the results of these trials, the combination etoposide and cisplatin is considered to be the standard treatment for patients with advanced seminoma. This is in contrast with the standard treatment for patients with disseminated non-seminomatous germ cell tumors, being the combination of bleomycin, etoposide and cisplatin, even in good prognosis patients. Two randomized studies have stressed the importance of bleomycin in the treatment of good prognosis patients. However, although both studies included seminoma patients, the percentage was too low, 6–8%, to conclude whether this was also true for seminoma patients.[55,56] Other cisplatin-based combinations have a comparable efficacy, but induce probably more toxicity.

Single-agent carboplatin cannot be recommended as the first-line treatment because of a high failure rate, even the combination of etoposide and carboplatin is inferior compared to etoposide and cisplatin. Other carboplatin-based combinations yielded high response rates, but randomized trials comparing these combinations with EP are lacking.

The approach for patients with post-chemotherapy residual disease remains controversial. Resi-

dual disease less than 3 cm can be safely observed; residual disease larger than 3 cm shows persistent tumor in up to 30% and surgical evaluation of these residuals should be considered.

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