Commentary (Markus/Studer)—Testicular Cancer: What’s New in Staging, Prognosis, and Therapy

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The management of patients with clinical stage I nonseminomatous germ-cell tumors is still highly controversial. In a recent survey, urologists and oncologists were asked to state their choice of treatment for patients with clinical stage I nonseminomas who were at high risk for recurrence after orchiectomy. Not surprisingly, urologists chose retroperitoneal lymph node dissection over chemotherapy, while oncologists indicated a preference for adjuvant chemotherapy.[1]

Based on the results of this survey, one would expect that a review coauthored by a urologist and a medical oncologist would present a balanced view on this topic. However, in their interesting article, Foster and Nichols take a strong stand against the use of adjuvant chemotherapy. This viewpoint should be placed into broader perspective.

Shortcomings of Retroperitoneal Lymphadenectomy

Despite the fact that no randomized study has directly compared retroperitoneal lymphadenectomy to adjuvant chemotherapy in patients with clinical stage I nonseminomatous germ-cell tumors, retroperitoneal lymph node dissection is associated with various problems, which are generally understated. Although initial treatment with retroperitoneal lymphadenectomy usually produces a high cure rate, this is only possible because a significant proportion of patients also receive chemotherapy and are under strict surveillance.

In an average-risk population, approximately 20% to 30% of men with clinical stage I nonseminomas will be upstaged to pathologic stage II disease by retroperitoneal lymph node dissection.[2] Since disease is not confined to the retroperitoneum in up to 50% of these patients, administering two cycles of adjuvant chemotherapy is a valid treatment option.[3] An alternative approach in such patients is intensive surveillance, with chemotherapy given only in the event of relapse; this approach is predicated on the hope that the recurrence would be diagnosed early enough to offer a high likelihood of cure with three or four cycles of standard chemotherapy.

A study by Williams et al[3] seems to suggest equal cure rates with immediate adjuvant chemotherapy vs treatment at relapse in patients with stage II testicular cancer, but this study is relatively small. In a series from the Indianapolis group, 54% of patients with stage B testis cancer received adjuvant chemotherapy after retroperitoneal lymphadenectomy.[4] Without chemotherapy, 26% of the patients with even low-volume B1 disease relapsed. Overall, Baniel et al cite a 37% relapse rate for stage II patients who do not receive adjuvant chemotherapy, which is about the same as the 35% rate described by the same group after retroperitoneal lymph node dissection for clinical stage I disease.[2] Unfortunately, the Indianapolis group found that treatment was too late in 2 out of 18 patients, who died of testicular cancer.[4]

Another problem is that even in patients with pathologic stage I disease, about 10% will still relapse despite a negative retroperitoneal dissection. Again, this suggests the need for surveillance and at least three or four chemotherapy cycles in relapsing patients.

Thus, retroperitoneal lymphadenectomy, with its well-known associated perioperative and late morbidity,[summarized in reference 5] is an unnecessary major surgical procedure in 70% to 80% of the whole clinical stage I population. Moreover, lymphadenectomy findings lead to the use of additional chemotherapy in at least 15% to 30% of patients, depending on whether or not adjuvant chemotherapy is given to the whole pathologic stage II population. This will certainly augment chemotherapy-associated side effects, since about 25% of the patients will receive treatment for...
metastatic disease, which increases the necessary cycle number from two (adjuvant chemotherapy) to at least three or four cycles and is associated with significant fatal toxicity (see below).

**The Case for Adjuvant Chemotherapy**

These shortcomings of retroperitoneal lymph node dissection have increased the attractiveness of the concept of administering less chemotherapy earlier in an adjuvant setting. Several trials have examined the effect of two cycles of BEP (bleomycin, etoposide, and Platinol) in patients with clinical stage I nonseminomatous germ-cell tumor who are at high risk for relapse; of the 293 patients studied, only 6 relapsed.[5-7] Thus, the efficacy of this approach compares favorably to the cure rates reported after retroperitoneal lymphadenectomy. This is even more reassuring if one takes into consideration that patients in the chemotherapy studies were typically at high risk for relapse, as defined by vascular invasion or embryonal carcinoma histology in the orchiectomy specimen. Critics of the adjuvant chemotherapy approach are concerned mostly with its potential toxicity. However, these subjective concerns are not corroborated by the clinical experience with adjuvant drug treatment. Interestingly, in an editorial, Nichols and Foster themselves have cited the low toxicity of two cycles of BEP chemotherapy as an argument against deleting even bleomycin from this combination.[8]

Neither secondary leukemias nor the potentially lethal pulmonary toxicity of bleomycin have been observed with two cycles of BEP.[5-7] Secondary leukemias are largely confined to patients receiving etoposide at a total dose of more than 2,000 mg/m². The total dose of etoposide in two BEP cycles is 720 to 1,000 mg/m². In two reports comprising more than 800 patients receiving 1,500 to 2,000 mg/m² of etoposide, only 3 cases of probable secondary leukemia were reported.[7,9] In addition, the available literature indicates that adjuvant chemotherapy with BEP does not significantly increase the risk for sperm abnormalities, hearing loss, or subclinical lung toxicity.[5-7]

The toxicity of BEP is low only if two cycles are administered, however. Fatal toxicity has been observed in 2.8% of patients given three or more cycles of this combination,[10] and the significant negative impact of the fourth chemotherapy cycle on toxicity has been proven in a randomized trial.[11] These data provide an important argument against delaying chemotherapy until large-volume disease requires more chemotherapy cycles to provide an acceptable chance for cure. Thus, based on the available literature, it would seem that, given its safety and effectiveness, first-line adjuvant chemotherapy should be the preferred treatment option for patients with high-risk clinical stage I nonseminomas. Retroperitoneal lymphadenectomy alone is therapeutic in only about 15% to 20% of these patients; for the remaining more than 80%, it is a rather expensive diagnostic procedure that is associated with significant morbidity.

Does it follow that all patients with clinical stage I nonseminomatous germ-cell tumors should receive adjuvant chemotherapy? Probably not, since the probability for relapse is rather low in patients whose tumor shows no signs of vascular invasion or embryonal carcinoma in the orchiectomy specimen. These men probably can be managed by strict surveillance alone and treated with salvage chemotherapy or surgery in the rare event of relapse.

**The Surveillance Option**

The concept of surveillance for the whole population of patients with clinical stage I disease has also attracted much interest in recent years. Prospective clinical trials of surveillance, with treatment given only in the case of relapse, have shown long-term survival rates, which are comparable to results seen with primary chemotherapy or retroperitoneal lymph node dissection.[12-14] Since selection bias could have contributed to the good outcomes reported in these trials, surveillance should be compared directly against adjuvant chemotherapy in a large, randomized, multicenter trial.

Surveillance relies heavily on patient compliance, however, and can cause significant anxiety, which has been termed the “Damocles syndrome.” The frequent examinations remind the surveyed men of their cancer history and their continuing risk for relapse.[6] From our personal experience, most patients choose active treatment over anxious waiting if all of the available in-formation is thoroughly discussed with them.

This experience is corroborated by data from Cullen et al, which showed that even patients at relatively low risk for recurrence selected adjuvant chemotherapy. This was true of new patients and, even more importantly, of patients who had already been managed with surveillance, chemotherapy, or both.[15]
Conclusions

We believe that there are few arguments left to support the choice of retroperitoneal lymph node dissection over adjuvant chemotherapy. Future clinical research in this area should compare surveillance vs adjuvant chemotherapy and should try to to minimize chemotherapy. However, a caveat that should be kept in mind with respect to this highly curable disease is to avoid jeopardizing the current success rate with ill-considered management modifications.

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