Management of Germ Cell Cancer: Lessons Learned From a National Database

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The treatment of metastatic germ cell cancer (GCC) with cisplatin-based chemotherapy results in a cure in well over 90% of patients with good-prognosis disease according to the International Germ Cell Cancer Collaborative Group. Recent data indicate that the eventual cure rate is also improving in intermediate- and poor-risk disease and may be approaching 90% in expert centers. Managing treatment of young males with curative intent is a gratifying opportunity for every medical oncologist. Young oncologists who have often been involved in the treatment of patients with GCC during their fellowships at academic sites and who continue their career in community hospitals may wish to continue managing this type of patient. The pitfall, though, is that they are no longer working in an environment where they can engage in expert team discussions and, with rare exceptions, they work without a surgeon experienced in postchemotherapy (post-CT) resections and often without dedicated radiologists and pathologists. Consequently, the proper place for managing these patients remains controversial, and there is a continuing debate in both Europe and the United States on whether treatment of these patients in low-volume centers is appropriate. Two previous studies from leading expert centers in the United States are relevant in this regard. Both studies contained data on post-CT histology findings after treatment, either at the expert center from the very beginning or after having the chemotherapy administered in community hospitals and referral only at the time of the post-CT surgery. The authors felt that the higher rates of unfavorable histology (viable cancer of mature teratoma) were associated with the chemotherapy regimen that was used (ie, three cycles of bleomycin, etoposide, and cisplatin [BEP] or four cycles of etoposide and cisplatin), but it is more likely that outcome was associated with the time of referral and was worse for patients first seen at the time of post-CT surgery. Poorer outcome of patients referred for post-CT surgery might be attributed to differences in adherence to the protocol dose in the chemotherapy regimen as well as differences in the referral patterns for the subsequent surgery. This interpretation is supported by findings in a study led by the European Organisation for Research and Treatment of Cancer and the Medical Research Council in the late 1990s. In that study, we reported on the impact of the treating institution on survival of patients with metastatic nonseminoma. Data were analyzed for 380 patients treated in one of 49 institutions participating in a European Organisation for Research and Treatment of Cancer/Medical Research Council randomized trial of BEP versus a sequential regimen of bleomycin-vincristine-cisplatin followed by etoposide-ifosfamide-cisplatin. Institutions were divided into groups on the basis of the total number of patients entered onto the trial. Patients treated in the 26 institutions that enrolled fewer than five patients onto the trial had an overall survival that was statistically significantly worse (hazard ratio [HR], 1.85; 95% CI, 1.16 to 3.03; \( P = .01 \)) than that of patients in the 23 institutions that had entered at least five patients. The difference in overall survival between the groups with less than five and more than five patients approached 20%. The explanations for this difference were the relative dose intensity of the chemotherapy delivered, which was highly significantly different \( (P = .007) \) and the frequency of surgery for residual masses (35% v 48% for the groups with fewer than five and more than five patients, respectively) approaching statistical significance \( (P = .09) \) and death as a result of acute toxicity. Despite these noticeable findings, many of today’s patients, particularly those with good prognosis who have the best chances for being cured by the initial chemotherapy regimen are still being treated outside of expert centers.

In the accompanying article, Lauritsen et al report on the outcomes of all patients with GCC treated in Denmark between 1984 and 2007. In a large effort using the Danish National Patient Register and the Danish Testicular Cancer database for reference, the authors analyzed a comprehensive data set of 5,322 patients. As the authors indicate, the management of patients with metastatic GCC today is increasingly centralized in three university hospitals, whereas in past decades, many of these patients had been treated in community hospitals all over Denmark that used national guidelines for appropriate management. Hence, the report contains informative data on outcomes, relapses, and toxicities by first and subsequent lines of treatment in the real-world setting, which reflect practice in many European countries as well as in North America. A total of 1,685 patients received BEP treatment, 76% of whom were deemed good-prognosis patients via the International Germ Cell Cancer Collaborative Group. Treatment failed for a total of 268 patients who thus needed additional chemotherapy. Of these, 115 patients needed a third or even additional (up to eight) lines of systemic treatment, and 136 patients (51%) died as a result of GCC. Of note, a considerable number of patients, even in third or subsequent lines of treatment, received conventional-dose chemotherapy. Of 731 patients with seminoma who received radiotherapy for stage I (48%) or stage IIA or IIB disease (52%), 54 required BEP, some of whom required additional lines of therapy. Compared with patients who received one line of BEP, the 115 survivors who had received more than one line of...
treatment had increased risks of death (HR, 1.7), second cancer (HR, 2.6), gastric ulcer (HR, 3.6), renal failure (HR, 4.6), and neurologic disease (HR, 3.3), all statistically significant. Death that was not a result of GCC was mainly attributed to second cancers, cardiovascular disease, and direct treatment-related toxicities.

This database contains novel data on the excess toxicity caused by multiple lines of systemic treatment in this basically young and otherwise healthy patient population compared with one line of BEP alone. This is important information; in several recent debates on trial results and interpretation, it was argued whether intensifying first-line treatment (eg, adding paclitaxel to BEP and dose-intensified regimens) was justifiable in view of some additional toxicity. The current data seem to indicate that the salvage lines of treatment as well as post-CT surgery for those patients who eventually need it may result in a greater overall treatment burden for the intermediate- and/or poor-risk patient population, which is at higher risk for needing additional lines of treatment.

Without a true comparison of the databases on the outcomes of the patients treated in this multicenter community and academic hospital setting in Denmark and those obtained in expert centers, it is difficult to interpret the results. Nonetheless, the number of these predominantly good-risk patients for whom one line of BEP chemotherapy failed may seem unfavorable compared with existing data that indicate long-term disease-free survival of more than 90% after the initial chemotherapy regimen for patients with metastatic GCC who were treated in expert centers. Likewise, the number of patients who required BEP or even subsequent lines of salvage chemotherapy after adjuvant or curative radiotherapy for stage I/IIA or IIB seminoma is surprising, given that fewer than 3% of treatment failures are expected after adjuvant radiotherapy for stage I seminoma or low-volume metastatic seminoma. In addition, the ultimate outcome of the 268 patients requiring more than one line of treatment, with 51% of deaths being a result of GCC plus additional early and late complications, may seem worse compared with what would be expected by salvage treatment at high-volume centers. Of note, the report does not specify the numbers of patients treated at high-volume centers and patients treated in community hospitals that likely reflect low-volume centers. Because several academic sites in Denmark can be considered expert centers, it is likely that the overall initial and salvage results reported here were influenced by treatment in the low-volume centers.

It is precisely this combination of multiple relapses and documented excess toxicity caused by salvage regimens that should evoke new concern regarding the management of patients with GCC in a community hospital setting, typically including low-volume centers. As previously stated, what really matters is that the patients are young men who, with few exceptions, can be cured if treatment is done all at once in the right place; many relapsing patients can still be salvaged but, in that case, the burden of achieving cure has become much greater than might have been necessary if treatment had been done properly at first in the right place. Therefore, the Danish physicians involved should be complemented for their recent efforts in accomplishing centralization of GCC management in only three academic hospitals in Denmark. We should all follow their good example.

**REFERENCES**


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AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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