The Story of Second Cancers in Patients Cured of Testicular Cancer: Tarnishing Success or Burnishing Irrelevance?

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In some regards, the study by Travis et al. (1) on second cancers in long-term survivors of testicular cancer, reported in this issue of the Journal, is tantamount to unearthing a time capsule or encountering the forward ripple from a stone dropped in a pond long ago. This study is generally consistent with other reports from long-term cancer registries. In aggregate, these works demonstrate an indisputable increase in second solid tumors and leukemias in patients receiving treatment for germ-cell cancer. How should we respond? Should these data be greeted with a shrug and “so what,” or should they engage active tinkering with a very successful therapeutic program?

Reports from population-based registries have limitations that may misrepresent the risk of subsequent cancers. For example, the regular follow-up of patients with testicular cancer and an increased awareness of cancer in these patients may produce lead-time bias or the early diagnosis of potentially insignificant cancers (as may be produced by screening for prostate cancer using tests for prostate-specific antigen). It is more likely, however, that these registry studies underestimate the risk of secondary cancers. The incidence of second cancers may be falsely low because of miscoding of patients who experience a recurrence of their primary cancer. In addition, estimates may not be accurate in a young, mobile population that may move from the area encompassed by the registry. It is equally problematic to attempt to assign causality in patients who are not specifically followed as part of a clinical trial. Such patients have inadequate data regarding specific details of treatment (i.e., types of treatment and doses and durations of radiation therapy or chemotherapy). The study by Travis et al. exemplifies this difficulty by including patients from two registries without any information regarding treatment, and none of the patients in the study had specific information concerning the type or duration of primary or secondary therapy.

It is unfortunate that Travis et al. provide an incomplete picture of the risk of second cancers in patients with testicular cancer. By confining the database to those who received radiation therapy or chemotherapy, the baseline incidence of nontesticular cancers in patients treated with surgery alone is unknown. It is certainly possible (likely) that there may be common etiologic factors, genetic risks, or prenatal exposures that may be imposing a generally higher incidence of cancer in these patients. The recent recognition of an association between testicular cancer and disease caused by HIV-1 (human immunodeficiency virus type 1) opens up the possibility of associations with non-Hodgkin’s lymphoma, sarcomas, anal cancer, and others (2). Several investigators (3,4) have reported an increased risk of dysplastic nevi syndrome and/or melanoma in patients with testicular cancer. Others (5–7) have reported an association between acute megakaryocytic leukemia and primary mediastinal germ-cell tumors, including the presence of the isochromosome 12p in the leukemic cells of patients.

There is reason to hope that the results reported by Travis et al. represent “high tide” for the incidence of second solid tumors. Again, insufficient detail of treatment limits this speculation, but one can impute a lower incidence with modern therapy by remembering common treatment practices in this era that are just now falling out of general practice. Extensive radiation therapy, prolonged chemotherapy, and combinations of both were commonly employed. It is entirely expected that such treatment practices, as was the case for Hodgkin’s disease, breast cancer, and ovarian cancer, as well as for pediatric tumors, would be associated with an unacceptably high incidence of second cancers (8–12).

The specific use of radiation therapy and chemotherapy in the treatment of germ-cell tumors has evolved during the past few decades. In the 1960s, 1970s, and 1980s, classic alkylators used in the treatment of these cancers, such as cyclophosphamide, were also commonly employed in germ-cell tumor regimens. These alkylating agents are no longer commonly used in the treatment of advanced germ-cell tumors (13). Furthermore, the duration of chemotherapy often extended to 2 years (even in the adjuvant setting) in the early trials of therapy for testicular cancer as compared with the 9–12 weeks of treatment now used (14,15).

Radiation has been a well established and effective therapy for the treatment of early stage seminoma. Indeed, in an era before cisplatin-based combination chemotherapy, radiation therapy was the only treatment. As was the case for Hodgkin’s disease, extended ports (using prophylactic mediastinal radiotherapy [PMR]) became the standard of care for patients with stage IIB disease (16). The emergence of successful chemotherapy for disseminated disease and the recognition of late side effects, such as cardiovascular disease and second cancers, have led the most ardent supporters of PMR to abandon such an approach for patients with stage II disease (17–19).

The issues of secondary leukemia are more complex and more worrisome. Unlike the situation with second solid tumors, there is no impact of awareness, early diagnosis, or, for the most part, treatment. The contribution of etoposide to the safe and effective management of disseminated germ-cell tumors is in-
disputable (13,20). Unfortunately, it is also indisputable that etoposide, in the combination of chemotherapy given for germ-cell tumors, is uniquely responsible for the development of certain subsets of secondary leukemia (21–23). Etoposide will, rightfully, remain an essential component of germ-cell tumor chemotherapy and will be associated with a very small incidence of secondary leukemias (24).

So, with these imperfect data demonstrating a low incidence of second cancers, should we rethink our approach to the therapy of germ-cell tumors? Absolutely! The recognition that any treatment, even two cycles of chemotherapy or low-dose radiation therapy, is likely to be associated with a definable risk of second cancers should cause careful consideration of the relative benefits of such therapy. This consideration should call into question such practices as primary chemotherapy for stage I disease (50%–70% of patients receiving unnecessary chemotherapy), automatic chemotherapy for pathologic stage II nonseminoma (50%–70% of patients receiving unnecessary chemotherapy), and addition of radiation therapy for treatment of persistent masses in seminoma (0%–5% benefit). Approaches that diminish the possibility of requiring chemotherapy or radiation therapy should be considered, such as retroperitoneal lymphadenectomy in early stage nonseminoma and surveillance in early stage seminoma. There are also nonmalignant consequences of treatment that can be equally important and devastating. All of these treatment-related complications could be avoided by improved selection of patients for active surveillance or surgery-only protocols following orchietomy.

Once the most common cause of death from cancer in young men, testicular carcinoma is today the most curable of solid tumors. Approximately 95% of those diagnosed and appropriately treated should remain disease free. In this light, the study by Travis et al. is both sobering and provocative. Their observations challenge us to rethink our opinions about this “Model for a Curable Neoplasm” (25). Long-term follow-up with detailed accounting of specific treatments administered to patients with testicular cancer is needed. The treatment of germ-cell neoplasms has varied largely from patient to patient during the first three quarters of this century. Trials that have defined the minimal threshold of therapy for the majority of patients with this disease have only become part of the standard of care during the past decade. It is these data from the modern era that we are obliged to report carefully and to track longitudinally that will provide the contents of the next time capsule that should be opened on this subject.

References