Development of a prognostic model for patients with extragonadal germ-cell tumors

Germ-cell tumors (GCTs) are unique among solid tumors in their responsiveness to therapy and in the secretion of serum tumor markers (STMs), the latter providing the clinician with an easily accessible and accurate way of following tumor response to therapy. The staging of GCTs must be clinically relevant so that patients receive the most appropriate therapy that allows for maximal cure rate with the lowest possible levels of morbidity and mortality. A major goal of the International Germ Cell Cancer Collaborative Group is the development of a universal staging system that is: (i) simple, effective and widely applicable on an international scale; (ii) applicable in clinical trials; (iii) scientifically valid; (iv) includes both seminoma and nonseminoma; and (v) has been validated.

Staging is based on disease site of origin, histology, bulk of disease and STM levels. In this issue of *Annals of Oncology*, Hartmann et al. [1] investigate prognostic variables in patients with seminoma and nonseminoma extragonadal germ-cell tumors (EGCTs) to assist in the development of an outcome model. Patients with EGCTs were retrospectively evaluated from 11 centers in Europe and the USA from 1975 to 1996.

Extragonadal germ-cell tumors differ from GCTs of testicular origin in many ways [2–10]. First, the histological subtypes represented in adult EGCTs are different from those of primary testicular GCTs. The pure yolk-sac tumor is rare in primary adult testicular tumors but occurs frequently among anterior mediastinal GCTs. The same is true for pure choriocarcinoma, a rare form of testicular tumor, the frequency of which is disproportionately high in anterior mediastinal tumors. Sarcoma is also found infrequently in mixed GCTs of the testis, but more often in mixed GCTs arising in the mediastinum. In addition to the histological differences of these two types of GCTs, extragonadal tumors differ from testicular tumors in that congenital anomalies are uniquely associated with the extragonadal category.

Patients with EGCTs, in contrast to those with primary testicular tumors, characteristically present with far advanced disease, which poses challenging clinical problems. Only with intense therapy and meticulous supportive care do these patients have an opportunity for long-term, tumor-free survival [2, 7, 9–11]. Standard therapy that is curative for nonseminomatous GCTs of the testis does not achieve an equivalent high cure rate for anterior mediastinal tumors.

The clinical dilemmas confronting physicians treating patients with EGCTs differ from those faced when treating patients with primary gonadal tumors. One such dilemma is how to distinguish patients with primary EGCTs from those with a metastatic GCT of an occult primary testis origin [12, 13]. The occult teratoma syndrome is a clinical entity, which encompasses tumors that are either true EGCTs or differentiated tumors that have features compatible with, but not diagnostic of, GCTs and cannot be clinically distinguished from EGCTs. The distinction between these two conditions is a clinically relevant concern. Unrecognized occult primary testicular tumors may remain refractory to chemotherapy despite eradication of systemic disease, and patients with non-diagnosed disease mimicking a GCT have a poorer prognosis compared with their counterparts whose disease can be histologically identified.

To address the issue of EGCT treatment, it is necessary to separate patients into clinical categories that predict the likelihood of their GCT being of extragonadal origin. Patients in the EGCT category are those whose tumors have pathological features diagnostic of germinal origin, but their primary location is not the testicle, and their tumors are not sites of metastases from a testicular tumor. The most frequent primary locations of primary EGCTs are the anterior mediastinum, retroperitoneum and the pineal area. When a GCT with no clinical evidence of a primary testicular tumor is located in the retroperitoneum, it is likely to be associated with an occult primary testicular tumor [3, 4]. Even though its pathological features are diagnostic of a GCT, there is a high risk of it being an occult primary testicular tumor. Their outcome is similar to those patients with a known primary testicular tumor with metastatic retroperitoneal disease.

The final category of patients with EGCTs should include those patients whose tumors have pathological features compatible with germ-cell origin but which are not pathognomonic. These tumors have clinical features that are sometimes indistinguishable from EGCTs, but they are likely to be occult non-germinal tumors. Some patients whose tumors had pathological features compatible with, but not diagnostic of, GCTs and whose clinical picture was indistinguishable from that associated with GCTs had a high response rate but a low long-term disease-free survival rate. At autopsy, the majority of these patients were found to have non-germinal tumors originating in the lung or upper gastrointestinal tract. Elevated serum markers are not diagnostic of GCT origin. Although patients with non-germinal extragonadal tumors...
that mimic GCTs benefit from chemotherapy with prolonged palliation, they do not benefit from a significant cure rate.

Seminoma is characterized by distinct pathological features and a unique clinical picture. The metastatic spread of seminoma is predominately nodal and rarely hematogenous. In the presence of visceral involvement, their clinical outcome is inferior. The majority of patients treated for seminomas remain alive and disease free. The major clinical dilemma in treating seminoma is the selection of therapy for the minority of patients who require more aggressive upfront approaches [5].

These data reflect, in part, patients treated before the widespread availability of supportive care. The use of cisplatin-based chemotherapy has played a major role in the curability of this patient population. Although the need to identify new therapeutic modalities to improve the survival of patients with EGCTs from nonseminoma origin or from seminoma origin with visceral involvement still remains.

With the consensus review for EGCTs in this article, the hope for the future is to maximize the therapeutic benefit and decrease the morbidity of therapy for these patients based on this prognostic outcome model. Furthermore, the use of this prognostic model for all EGCT clinical trials will assist in the comparison of results.

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References