8. Germ Cell Tumors

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The assay of alpha-fetoprotein (AFP) [1] and of the β -subunit of chorionic gonadotro-pin (β -HCG) has become a routine procedure in the initial diagnosis and in monitoring therapy of patients with testicular cancer. These markers permit an effective assessment of the tumor growth rate, enable the prediction of prognosis and assist the pathologist and clinician in staging; finally, sequential assays are essential in the subsequent management of the patient [2–6]. It is essential to measure both these markers since one or the other or both may be elevated. During therapy, the tumor cell population may change and result in the expression of different β -HCG/AFP patterns than initially observed. Immunohistochemical staining has been used successfully to establish the origin of metastatic tissue of unknown origin and in establishing the tumor types [7, 8]. There are now numerous attempts to improve the specificity and sensitivity of the assays by the use of monoclonal antibodies. The need for, and importance of, improved sensitivity and specificity requires to be stressed. Elevations of AFP, β -HCG or both are seen in about 90% of patients with nonsemi-nomatous testicular cancers. In less than 20% of individuals with seminomas, β HCG will be elevated due to the presence of syncy-tiotrophoblast cells which are responsible for its biosynthesis. It should be emphasized that positive marker values are a presumptive evidence of the presence of a cancer; a negative value should not be used to rule out its presence. When the tumor is successfully removed, blood levels should fall with a half-life for β HCG of 16–24h and for AFP of about 4.5 days. In our institute, successful therapy is defined as a return of both markers to normal levels. With the methods used in our laboratory, the normal reference level of β HCG is less than 2 ng/ml and of AFP less than 10 ng/ml. It is essential for each laboratory to establish its own normal range not only because of possible methodological differences, but also of geographical differences in populations.

A great variety of other tumor markers has been studied in testicular germ cell cancer. Among these are carcinoembryonic antigen (CEA), α -1-antitrypsin, pregnancy-specific β -glycoprotein, lactic dehydrogenase (LDH) and its isoenzymes, and an early Germ Cell Tumors

pregnancy factor-like substance [9]. Our own experience has only been with CEA and LDH. We have not observed any great use for CEA either alone or as part of a multivar-iate analysis in the management of these patients. Elevations of CEA are observed in about 20–30% of patients.

Placental-like alkaline phosphatase has been found to be a useful indicator of pure seminoma, whereas elevations of HCG and AFP indicate the presence of nonseminomatous cancerous elements [10].

We have attempted to use a grouping of clinical, laboratory and histopathologic factors in a multivariate analysis to predict response to therapy [11, 12]. LDH and β -HCG were the most significant parameters in the equation which was developed by our biostatistics laboratory. CEA and AFP did not add to the ability to discriminate responders from nonresponders. The only nonlaboratory factor of use was the total number of metastatic sites (TOTMET; none, 1, 2 or more). When these factors were used, the probability equation

indicated failure to respond to VAB therapy (vincristine, adriamycin, bleomycin) when values less than 0.5 were obtained and response to therapy with values greater than 0.5. The multivariate equation was

$$h = 8.514 - 1.973 \log(\text{LDH} + 1) - 0.530 \log(\text{HCG}) - 1.111 \text{ TOTMET}.$$

When this equation was evaluated in 171 patients, it predicted that 121 patients would respond. Of these 121 patients, 114 (94%) actually did respond. It also predicted that 50 patients would not respond, but of these only 28 (56%) did not respond. The overall prediction rate was 142 of 171 patients or 83%. Using the equation with an independent set of data collected at another institution, the model correctly predicted responses in 36 of 42 patients (86%) and in 5 of 7 patients who did not respond, i.e. an overall prediction rate of 41/49 (84%). The usefulness of such a model in a disease which is highly curable is in the identification of those individuals who are unlikely to do well and to consider alternate or additional therapy, initially.

In another study from our institution, the response to therapy was related to the markers in 103 patients with advanced germ cell tumors (stage III and bulky unresectable stage II nonseminomatous germ cell tumors). Of 13 patients who had neither marker elevated 12 (92%) had a complete remission compared with only 15 of 28 patients (54%) who had only β -HCG elevated, 10 of 23 (42%) who had only AFP elevated and 25 of 36 (69%) who had both markers elevated. Some patients with elevated markers, who responded poorly to chemotherapy, had their response improved significantly by surgery. Values of AFP or β -HCG above 1,000 ng/ml indicated a poor prognosis.

A Medical Research Council Working Party [13] has reported survival data related to the size of the tumor and serum AFP and HCG concentrations. Low levels of markers were defined as AFP levels < 500 KU/l and HCG values < 1,000 IU/l. In patients with small tumors (< 2 cm) and low marker levels, the 3-year survival was 91%, but only 69% when the marker levels were elevated.

In patients with large tumors (2–5 cm), the survivals were 80% in individuals with low marker levels and 70% in those with high marker levels. In very large tumors (> 5 cm), the 3-year survival was 69% in

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patients with low concentrations of markers, but only 47% in those with high marker concentrations.

Testicular cancer is one of the few examples where the remarkable improvement in cure rate is directly related to the availability of tumor markers which allow precise analysis of the state of the disease and better patient management.

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