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Letter to the Editor

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THE RECENT editorial by Doctor Einhorn, 'Have aggressive chemotherapy regimens improved results in advanced germ cell tumors' (Vol. 22, No. 11, November 1986), is deserving of comment.

Doctor Einhorn has questioned the merits of newer and more aggressive chemotherapy regimens for the treatment of patients with germ cell tumors. In his review, he analyzes the clinical data that are available and concludes that there is no evidence to support the use of these more toxic regimens. His conclusions are based on three points: (1) the improving survival of patient with germinal tumors treated with PVB in more recent years, (2) the toxicity of the newer regimens and (3) the absence of an improved survival with these newer regimens when compared by tumor volume. In addition, it is suggested that there is no potential for an increased cure fraction with the introduction of more intense chemotherapy for patients with teratoma. Each of these issues needs to be addressed separately.

An improved survival among patients treated with germ cell tumors has been reported in recent years. This improved survival has been attributed to the clinical presentations of patients currently treated, the acquired experience with chemotherapy and the more appropriate integration of chemotherapy and surgery.

A factor that may give the false appearance of an improved survival is the recent change in the staging systems. The initial staging system developed by Samuels *et al.* noted the inverse relationship between long term survival and tumor volume. The Samuels staging system was developed in an era when computerized tomography was not available and surgery was routinely performed among patients with retroperitoneal metastases. In our experience the portion of patients with unresectable abdominal presentations is increasing. We attribute this to the routine use of computerized tomography and the increased confidence urologic surgeons have in the ability of chemotherapy to eradicate retroperitoneal disease. As the confidence in the curative potential of chemotherapy has increased, the futile surgical attempts at reducing tumor volume or resecting large retroperitoneal masses prior to chemotherapy are becoming less frequent. We have adopted a 10 cm max. dia. as the discriminating line between clinical stage II and stage III disease. The validity of this staging system is supported by the differences in survival of patients with clinical stage II disease and those with advanced abdominal presentations.

The Indiana University experience offers a unique opportunity to evaluate the relevance of present staging systems. Following the introduction of PVB at the University of Indiana, no major therapeutic improvement has been noted. A series of randomized trials failed to note a survival advantage for the addition of maintenance vinblastine, with the addition of low dose adriamycin, or when BEP is compared to PVB. Despite the lack of an improvement in chemotherapy, recent studies show an improved survival when compared to the initial studies. We believe the major reason for this improved survival is the inclusion of patients in the recent studies who previously were included in stage II disease. The category of 'unresectable nonpalpable abdominal disease' is included in the clinical stage II patients at other institutions. Such patients have a near universal survival, and were likely included in the adjuvant series in the preCT scan era. The lack of maintaining discipline in separating these two categories has not only given the false impression of improving chemotherapeutic results, but also has obscured the fact that patients with truly advanced presentations continue to have a very poor prognosis.

Despite the difficulties with interpretation of clinical data as they currently are reported, there

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remains sufficient evidence to support the superiority of more recent chemotherapeutic regimens compared to standard therapy. I will restrict the remainder of this comparison to $CISCA_{II}/VB_{IV}$ and PVB for the purposes of this discussion: (1) Acute toxicity of $CISCA_{II}/VB$ is greater than that with PVB. Acute toxicity is directly related to bone marrow toxicity and mucosal injury from chemotherapy. By its nature, acute toxicity is completely reversible. Fatal complications of $CISCA_{II}/VB_{IV}$ are rare in our hands. Chronic toxicity is more related to the total dose of each individual drug used and the manner with which it is delivered. Clinical bleomycin pulmonary toxicity is not a problem for patients treated with $CISCA_{II}/VB_{IV}$. Pulmonary toxicity of PVB-treated patients is a significant cause of morbidity and occasional mortality. In addition, chronic vascular complications of therapy related to PVB (Raynaud's phenomenon, myocardial infarctions, cerebral vascular accidents) appear to be reported at a frequency higher than we see among $CISCA_{II}/VB_{IV}$-treated patients. Only a single patient has suffered a clinical Raynaud's phenomenon. Chronic toxicity by its nature is unlikely to be irreversible and likely to influence the patient's long term survival. (2) Yolk sac tumors represent very poor prognostic tumors when treated with PVB. The majority of patients treated with yolk sac tumors died of their disease. Any therapeutic advantage of $CISCA_{II}/VB_{IV}$ over PVB would be seen in patients with the poorest prognostic tumors. Seven of nine patients with pure yolk sac tumors are alive and disease-free when treated with $CISCA_{II}/VB_{IV}$. (3) Pathologic findings following chemotherapy with $CISCA_{II}/VB_{IV}$ significantly differ from those with PVB. Viable carcinoma among patients treated with $CISCA_{II}/VB_{IV}$ at postchemotherapy exploration is virtually nonexistent. This occurred at a frequency of approx. 30% in different series of patients treated with PVB. The difference in the frequency of postchemotherapy viable carcinoma can only be attributed to differences in chemotherapy. (4) Postchemotherapy teratomas have a behavior totally different among $CISCA_{II}/VB_{IV}$-treated patients than those treated with PVB. Although patients treated with PVB are frequently found to have sarcomatoid transformations of their teratoma, this histological subtype is not found in $CISCA_{II}/VB_{IV}$ treated patients. Sarcomatoid transformation is associated with a high relapse rate. Almost one-third of patients adequately resected and found to have a mature teratoma following treatment with PVB will subsequently metastasize. None of the patients treated with $CISCA_{II}/VB_{IV}$ and adequately resected have subsequent metastases (minimum follow-up beyond 3 years).

Where available data can be compared (postchemotherapy pathological findings, poor prognostic tumors), $CISCA_{II}/VB_{IV}$ is superior to PVB. The successful use of $CISCA_{II}/VB_{IV}$ requires adequate support facilities to maintain patients through acute myelosuppression and its side-effects and clinicians experienced in the management of these complications. It is our belief that patients with advanced germ cell tumors treated in such an environment benefit from the use of $CISCA_{II}/VB_{IV}$ with an improved survival and reduce long term morbidity.