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Guest Editorial

Second Malignant Neoplasms in Hodgkin's Disease

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With the advent of combined-modality therapy for Hodgkin's disease (HD), the prognosis has altered dramatically. Approximately 75% of all patients with advanced HD who are treated with combination chemotherapy can achieve a complete remission, and over half of these may be considered cured [11]. The prolonged survival, however, has led to the recognition of an increased risk of second tumor induction.

Widespread HD is associated with severe depression of cellular immunity [32] and this is adversely correlated with survival [33]. The concept of immunological surveillance is widely accepted and supported by circumstantial evidence. Thus tumors are more common in patients with both cellular and humoral immunologic defects [12, 36], and in immunosuppressed organ homograft recipients the risk of a second neoplasm appears to be increased 100-fold [24, 25]. It is also well recognized that patients with one cancer are at increased risk of developing subsequent neoplasms [20]. Although the immunologic abnormalities associated with active HD are a potential contributing factor, the true intrinsic risk of a second malignancy in HD cannot be assessed as there are no large groups of untreated patients. There are, however, reports of the two malignancies diagnosed simultaneously [6, 30, 34], but obviously two separate diseases may co-exist by chance.

Moertel and Hagedorn [19] found 13 second malignancies in 826 HD patients, Razis et al. [26] noted 24 in 1102 patients, and Belpomme et al. [2], 18 in 800 HD patients. None of these authors assessed the significance of their findings. Whitelaw [37], with 13 second malignancies in 210 patients, did not consider the relationship to be significant. Berg [3] confirmed the unexplained increase in Kaposi's sarcoma, but apart from skin tumors the incidence of other malignancies was no greater than that expected in the general population.

Arsenau et al. [1] noted a significantly increased risk of development of second malignant neoplasms, with the greatest increase in the 35 patients receiving both intensive radio- and chemo-therapy. Canellos et al. [7] noted a 23-fold increase in observed tumors over expected in the heavily treated sub-group. The majority occurred in the group where HD relapse occurred between intensive radiotherapy and subsequent intensive chemotherapy. Toland et al. [35], however, found that 10 of 11 patients in their series developed the second malignancy while still in their first complete remission at a median interval of 2.5 years from the diagnosis of HD. Pajak et al. [23], reporting 19 acute nonlymphocytic leukemias (ANLL) in 1325 patients, found that almost half occurred in patients in complete remission. All of Belpomme's [2] patients were in remission, and the second malignancy was the cause of death in seven of the eight who died.

The only consistent statistically significant second malignancy has been ANLL [2, 7, 8, 28, 35], and there is an unexplained increase in Kaposi's sarcoma [2, 3]. Recently we have reported two anaplastic carcinomas of the thyroid in patients with cervical irradiation and prolonged survival [14, 15]. Comparison of the observed and the expected ratio shows that the occurrence of this tumor is highly significant ($p < 0.005$). Although there appears to be a statistically significant increase in all solid tumors in some series, no other single tumor type appears individually increased in frequency. In contrast to HD, six of nine second malignancies in 40 treated myeloma patients were adenocarcinomas of the colon [4].

The etiology of second malignancies is multifactorial. The impaired cellular immunity of patients with HD and the further immunosuppressive effects of treatment provide an uniquely receptive milieu for the oncogenic cellular effects of radiation and chemotherapy. Radiation-induced tumors have been extensively studied fol-

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lowing both therapeutic [9, 17, 29] and military irradiation [5, 10, 31]. Alkylating agents can induce leukemia and other tumors [18, 27] and procarbazine has been shown to be carcinogenic in experimental animals [22]. The incidence of second tumors is directly related to the intensity of the therapy [1, 2, 7, 35] except in thyroid carcinoma where the response may be biphasic [15]. Although ANLL has been reported in patients treated with chemotherapy only, the combination of chemotherapy and irradiation seems most oncogenic. Our own group [13] of 503 treated HD patients from the pre-intensive therapy era produced 18 second neoplasms but no cases of ANLL. It is noteworthy that long-term maintenance chlorambucil was the most common factor in patients developing ANLL in complete remission in the CALGB study [23]. In a literature review of patients with nonneoplastic diseases with immunosuppressive agents, at least 45 of 58 patients who developed acute leukemia of various types had received alkylating agents [16].

Neufelt et al. [21] noted that all their patients had mixed-cellularity HD although this cell type represented only 28% of their total, but data from Toland et al. [35] and from CALGB (T. F. Pajak, personal communication) do not support this observation.

Patients treated now for HD have a long life expectancy, associated with a significantly increased incidence of ANLL and Kaposi's sarcoma and a somewhat increased incidence of a heterologous group of tumors. There is no proven correlation with any other individual tumor type, although we have postulated a relationship with anaplastic carcinoma of the thyroid. Tumor development appears to be related to abnormal cellular immunity and the intensity of treatment, which in turn has an influence on the immune system. It behooves us to continue aggressive induction therapy for HD, as the small risk of a second malignancy is negligible compared with the anticipated prolongation of life. However, therapy should be the minimum known to be effective for the cell type and stage of disease, and the details of such treatment in carefully randomized trials remains of great importance. Adjuvant chemotherapy in addition to radiotherapy for early-stage (I and II) disease remains an unproved modality. The preferred treatment for Stage III HD remains controversial. While regional radiotherapy in addition to chemotherapy for Stage IV HD has been recommended, it has not yet been proven superior to chemotherapy alone. While prolongation of chemotherapy to over six cycles of MOPP or similar combinations may be of value, there does not appear to be any place for prolonged maintenance therapy, especially with an alkylating agent.

Any patient who has received mantle or local cervical irradiation should have routine thyroid palpation at each visit. Should a thyroid nodule be found that fails to disappear on suppressive therapy, surgical intervention is required.

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