Recent Results in Cancer Research

Lymphoid Neoplasias II

Clinical and Therapeutic Aspects

Edited by
G. Mathé M. Seligmann M. Tubiana

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Part I

Clinical Aspects: Staging and Therapeutic Implications

Introductory Remarks

M. TUBIANA

The aim of these last two sessions is to assess to what extent recent pathologic and biologic considerations can be used for diagnosis and treatment. This morning's session is devoted to staging. Staging constitutes one of the major advances of the last decade for malignant lymphoma. As a result of speculations about the propagation of this disease, laparotomy was introduced by the Stanford group. In turn, laparotomy and modern staging have provided important information on the natural history of malignant lymphoma. In particular, the incidence of occult involvement of spleen in Hodgkin's disease or of bone marrow in non-Hodgkin's lymphoma is much higher than previously suspected.

Much information has now been collected, and in light of 10 years' experience, we must now ask ourselves two questions: 1) what do we expect from staging laparotomy and 2) in which patients is staging laparotomy legitimate, i.e., when do the benefits outweigh the cost? The complications of laparotomy are not negligible, in particular for aged patients. Furthermore, laparotomy increases the therapeutic burden; for instance, the incidence of side-effects after abdominal irradiation is higher for those patients who have had laparotomy, a point that shall be discussed this afternoon.

Staging has three purposes: to provide prognostic indicators, to provide guidance for treatment, and to treat the spleen. Since a few papers will be devoted to staging in non-Hodgkin's lymphomas, I shall illustrate those points with Hodgkin's disease data. A controlled clinical trial was carried out by the radiotherapy-chemotherapy group of EORTC from 1971–1976. The protocol was the following. All patients with Hodgkin's disease, clinical stages I and II located above the diaphragm, were randomized between staging laparotomy and splenectomy or no laparotomy. After laparotomy, irrespective of the results of the pathologic study of the spleen and the biopsy of the para-aortic lymph nodes, an irradiation of the para-aortic lymph nodes was carried out. For those patients without laparotomy, an irradiation of the spleen was also performed. Subsequently, for those patients with mixed cellularity or lymphoid depletion histologic types, chemotherapy was performed regardless of the results of the staging laparotomy. This trial had two aims: 1) to compare splenectomy and splenic irradiation and 2) to assess the prognostic significance of the information provided by laparotomy. This is why, in order to reach these goals, all patients received the same treatment without taking into account the results of the splenectomy or the para-aortic lymph node biopsy. Two hundred and ninety-five patients were included in this cooperative trial, and only one patient had another treatment protocol because the liver biopsy was positive.

The preliminary results of the trial will be published by the EORTC Radiotherapy-Chemotherapy group, and I shall only briefly summarize them. There is no difference in the survival or the incidence of recurrence between the two groups: 1 death and 21 recurrences out of 114 patients with laparotomy and 2 deaths and 21 recurrences out of 108 patients without laparotomy. Splenectomy and spleen irradiation appear to be equivalent. In the group with laparotomy, it is interesting to compare patients with or without spleen involvement. In those patients without spleen involvement (68 patients), six recurrences were located in an irradiated area, none in a nonirradiated lymphatic area, and six were extranodal recurrences. In the group with spleen involvement (26 patients), the incidence of recurrence in an irradiated area was

comparable (two patients), but the recurrence in nonirradiated lymphatic area was much higher (five patients); on the other hand, the incidence of extranodal recurrence was not increased (two patients). These data show that spleen involvement has a significant prognostic value. But contrary to what was expected, they suggest that it is more an indicator of lymphatic spread than of extranodal dissemination.

On the basis of these data and the statistical analysis of a previous controlled clinical trial, a new trial was designed with the aim of distinguishing two groups of clinical stages in Hodgkin's disease: one with a favorable prognosis, for which a minimal treatment might be sufficient to obtain a high proportion of cure, and another group, for which a more aggressive treatment including multiple courses of polychemotherapy is performed, despite its side-effects on gonads and bone marrow. In the first group are included clinical stages I and II with all the following requirements: age below 40 years, a good histologic subgrouping (lymphoid predominance or nodular sclerosis), ESR below 70 mm/h, and pattern of presentation with mediastinal involvement (for clinical stage II). All these patients are submitted to diagnostic laparotomy and splenectomy. They are included in the good group only if they remain at pathologic stage I or II after laparotomy.

Laparotomy is not performed for the other patients for whom polychemotherapy seems to be required anyway. Hence, in this new trial, laparotomy is used for selecting a group of patients with a good prognosis and for whom a minimal treatment might be sufficient. It is hoped that it will make it possible to avoid polychemotherapy or irradiation of the pelvis in some young patients and consequently reduce damage to the gonads and decrease the genetic burden.

Unfortunately, many years will be necessary to evaluate the validity of this approach, Nevertheless, it stresses the present tendency toward reducing, at least for some patients, the cost of treatment.

Cellular Renewal Kinetics of Malignant Non-Hodgkin's Lymphomas

K. BREMER

To maintain the cellularity of the human lymphatic system at its normal level, the rates of lymphocyte production and death apparently must be equal. This steady-state equilibrium is the result of complex regulatory mechanisms of the micro- and macroenvironment including direct cellular interactions, antigenic stimulation, and biochemical and humoral influences [39]. To give rise to the development of malignant lymphomas, the production rate of the neoplastic lymphocytes must exceed their death rate. In contrast, if malignant transformation of lymphocytes is associated with higher death rates than production rates, these neoplastic cells eliminate themselves due to this suicidal proliferative constellation. These considerations may elucidate the decisive importance of lymphocyte proliferation kinetics for the development of malignant non-Hodgkin's lymphomas (NHL).

Proliferating Lymphoma Cells

Using labeled DNA precursors such as ^{3}H-thymidine (^{3}H-T), recent studies of lymphocyte proliferation kinetics in man confirmed previous animal-derived data showing that usually only large basophilic lymphoid cells (immunoblasts, large germinal center cells = centroblasts, plasmoblasts, large and medium-sized lymphocytes = lymphoblasts) actively synthesize DNA and divide, also giving rise to smaller cell variants of limited or no proliferation capacity [39, 40].

Cell Cycle Parameters of Lymphoma Cells

For normal human large basophilic lymphoid cells, an average generation time of about 24 h and DNA synthesis time of usually 10–12 h have been determined (Table 1). These two cell cycle parameters, which are of great importance for characterization of cellular proliferation kinetics, exhibited considerable time variation in normal cells and even more in the different lymphoma cells. With the exception of Burkitt's lymphoma cells, however, the generation time of NHL cells generally revealed a tendency to be prolonged, whereas the majority of the DNA synthesis times of the neoplastic cells were found to be within the normal range. This indicates that the prolonged generation time is mainly caused by an extended postmitotic G_1-phase. Furthermore, to initiate growth of malignant lymphomas, it must be postulated that this prolonged cellular generation time is overcompensated by an even longer than normal life span of these neoplastic lymphocytes; thus, the production rate of lymphoma cells exceeds their death rate.