Review

Treatment of grey zone lymphomas

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Summary

The inability of distinguishing difficult cases of Hodgkin’s disease from non-Hodgkin’s lymphoma has been a long-standing problem. Initially, the controversy centered on lymphocyte-depleted Hodgkin’s disease; now with improved diagnostic techniques, most controversy centers around the anaplastic large-cell lymphomas. These problematic cases may also represent a less frequent problem, although data on this point is difficult to obtain. The future controversy may well involve the separation of T-cell rich B-cell lymphoma and Hodgkin’s disease, nodular paragranuloma type. Fortunately, to date the clinical data does not support that there is a major difference in therapeutic results depending on whether these cases are treated as Hodgkin’s disease or non-Hodgkin’s lymphoma.

Key words: grey zone lymphoma, Hodgkin’s disease, non-Hodgkin’s lymphoma

Introduction

At the Fourth International Symposium on Hodgkin’s Lymphoma, Cologne, Germany, 28 March through 1 April 1998, a workshop was organized on the histopathology of Hodgkin’s disease including lymphocyte predominant Hodgkin’s disease and grey zone lymphomas. The pathologists will separately report the results of that workshop and will attempt to define the pathologic entities that have been diagnostic problems.

The term ‘grey zone lymphoma’ appears to require some definition. In fact, grey zone lymphoma is not separately listed in the index of general oncology or even lymphoma textbooks [1]. A search of standard reference databases including Medline from 1966–1998 and Cancerlit from 1983–1998 by the LMIN system (Loyola Medical Library Information Network) failed to reveal any references. For the purpose of this discussion I will define ‘grey zone lymphoma’ as any lymphoma that cannot reproducibly be assigned to a given diagnosis of the Revised European–American Classification of Lymphoid Neoplasms (R.E.A.L. Classification) [2] by a group of expert hematopathologists.

Additionally, the clinician would like to know that the distinction being made had some clinical relevance, i.e., treatment or results would change for a given patient if one or the other diagnosis being considered were made. This author was asked to review his experience and the clinical literature describing the treatment of grey zone lymphomas. The results of that review are presented in this article.

Diffuse large-cell lymphoma vs. Hodgkin’s disease

Obviously, one of the most fundamental distinctions that must be made regarding any lymph node biopsy is whether it represents Hodgkin’s disease or non-Hodgkin’s lymphoma. In the past, these difficult distinctions involved cases that represented either diffuse large-cell lymphoma or lymphocyte-depleted Hodgkin’s disease. Almost all clinical decisions appear to diverge depending on the results of that distinction. Yet, what is the result of a retrospectively perceived error in the diagnosis of those two disease entities? What are the clinical results of treating non-Hodgkin’s lymphomas with a Hodgkin’s disease treatment program or Hodgkin’s disease with a non-Hodgkin’s disease treatment program?

One of the earliest experiences with this problem was defined in 1975 in the initial publication from the Medicine Branch of the National Cancer Institute that described advanced diffuse histiocytic lymphoma as a potentially curable disease [3]. All 27 patients in the report had their pathology reviewed and were felt to have non-Hodgkin’s lymphoma. Four of the 10 (40%) patients who were treated with MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) chemotherapy achieved a complete remission, while 7 of 17 (41%) patients who were treated with C-MOPP (cyclophosphamide substituted for nitrogen mustard) achieved a complete remission. Furthermore, later follow-up revealed no difference in the long-term survival of the MOPP or C-MOPP groups of patients [4]. In spite of these seemingly equivalent results, MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) was developed and utilized extensively for Hodgkin’s disease [5], while cyclophosphamide substituted MOPP or C-MOPP was used for non-Hodgkin’s lymphomas since
cyclophosphamide was felt to be a more active drug than nitrogen mustard in that disease [6].

CHOP chemotherapy (cyclophosphamide, Adriamycin, vincristine, and prednisone) has been established as the current standard therapy for aggressive non-Hodgkin’s lymphomas [7]. The reported use of CHOP in Hodgkin’s disease has been limited. In 1983, Miller and colleagues reported the results of a Southwest Oncology Group trial (SWOG-7961) [8]. This two institution pilot study treated 12 patients with Hodgkin’s disease. All patients had objective responses with three (25%) achieving a complete response and nine (75%) a partial response. After a median follow-up of 32 months, the median response duration was 13.5 months and the median survival had not yet been reached. While the number of patients was quite small, the results suggested that the use of CHOP chemotherapy in Hodgkin’s disease was not optimal.

Thus, while there is obviously no proof that failure to correctly diagnose diffuse large-cell lymphoma vs. lymphocyte-depleted Hodgkin’s disease resulted in inferior therapeutic results, common medical practice does treat these entities differently and may have different outcomes. New immunologic and genotypic studies may have significantly improved the pathologist’s ability to accurately make these distinctions.

Anaplastic large-cell lymphoma vs. Hodgkin’s disease

The R.E.A.L. Classification [2] includes anaplastic large-cell lymphoma (T- and Null-cell types) as defined entities under the category of ‘T-cell and putative natural killer cell neoplasms’. A provisional entity was described as anaplastic large-cell lymphoma Hodgkin’s-like (Hodgkin’s related). The Lymphoma Committee of the Southwest Oncology Group has attempted to investigate this area by retrospectively reviewing two large clinical trials of advanced stage, large-cell non-Hodgkin’s lymphoma and Hodgkin’s disease to determine the incidence of these entities and the resultant prognosis [9]. We reviewed the pathology and clinical features of 573 evaluable patients from SWOG-8516 (A randomized comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin’s lymphoma) [7]. Seventy-three cases (13%) were found to have anaplastic morphology. The overall survival of these patients was similar to that of the remaining patients with large-cell lymphoma (P = 0.45). These cases were further subdivided into 42 cases (7%) of classic anaplastic large-cell lymphoma and 31 cases (6%) of Hodgkin’s disease-like anaplastic large-cell lymphoma. The cases with Hodgkin’s disease-like anaplastic large-cell lymphoma had improved survival compared to those cases with classic anaplastic large-cell lymphoma, but they also had more favorable prognostic features. When the two groups were adjusted for prognostic features as defined by the International Prognostic Factor Project [10], the survival benefit disappeared.

We also reviewed the pathology and clinical features of 467 valuable patients from SWOG-7808, a study of low-dose involved field radiation after MOPP-BAP chemotherapy for patients with advanced stage Hodgkin’s disease [11]. Only eight (2%) patients were found to have Hodgkin’s-like anaplastic large-cell lymphoma, demonstrating that this is an uncommon entity in patients diagnosed with Hodgkin’s disease. Furthermore, the median five-year survival of the 459 patients with Hodgkin’s disease was 77% vs. 63% for the eight patients with Hodgkin’s-like anaplastic large-cell lymphoma.

Zinzani et al. have conducted a randomized trial of ABVD versus MACOP-B with and without radiation therapy for patients with anaplastic large-cell lymphoma, Hodgkin’s-like [12]. Twenty-one patients were randomized to receive ABVD and 19 patients were randomized to receive MACOP-B. The complete response rate was 90% in each arm and after 32 months of median follow-up, the relapse-free survival and overall survival between the two arms were identical.

Both of these studies suggest that there is no clear clinical rationale for the provisional entity described as anaplastic large-cell lymphoma Hodgkin’s-like (Hodgkin’s related), nor is there evidence that the prognosis differs when those cases are treated as Hodgkin’s or non-Hodgkin’s lymphoma.

Miscellaneous grey zone lymphomas

The pathologists in the accompanying workshop report are also attempting to distinguish between T-cell rich B-cell lymphoma and Hodgkin’s disease, nodular paragranuloma type. Unfortunately, there is no currently available clinical data to support or refute the importance of these distinctions.

References


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