

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Advances in the Treatment of Hodgkin Lymphoma

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H&O What are some of the unique epidemiologic characteristics of Hodgkin lymphoma that have led to insights into the etiology of the disease?

PM The etiology of Hodgkin lymphoma is an area that has been difficult to research. It has been extraordinarily difficult to grow Hodgkin lymphoma in cell lines. The very few examples of successful cell lines often come from very advanced cases, in which the cells are probably already altered and thus atypical of most patients. There are no mouse or other animal models for Hodgkin lymphoma, so it cannot be studied in that setting. It took many years to figure out what the primary cell of origin of Hodgkin lymphoma is, and it is now determined to be a B cell.

Some data suggest that viral infection, which would normally have a fairly benign clinical presentation in childhood but can have a more severe virulent manifestation in the late teenage or early adult years, can lead to this disease. Some examples are mononucleosis or mumps, both of which are fairly significant and toxic to adults but not severe in children. There are also some data suggesting that Epstein-Barr virus (EBV), which can transform B cells into malignant cells, is a potential candidate for the development of Hodgkin lymphoma. EBV is known to associate with the development of Burkitt lymphoma, and it may be implicated in Hodgkin lymphoma. Genetic material from EBV can be found in the malignant Hodgkin cells, which does not prove causation because that material could be a bystander, but it is nevertheless present in approximately 50% of cases. The presence varies by age and histologic cell type. Additionally, some serologic data tends to support the hypothesis that EBV may be causing

Hodgkin lymphoma. Furthermore, epidemiologic data suggest that patients who develop Hodgkin lymphoma are often from highly educated families with limited numbers of children growing up in single-family houses, suggesting that early exposure to different viruses might decrease the chances of developing this disease. These data lend support to the hypothesis that Hodgkin lymphoma is a more severe manifestation of a viral illness that causes a transformation to a malignant cell. Notably, Hodgkin lymphoma is almost always found in the neck or lower neck/chest, which are potentially primary if not secondary sites of respiratory illness, including routine viral illness. These discoveries have not, to date, been particularly helpful in developing treatment strategies.

H&O Can you discuss the new World Health Organization classification of nodular lymphocyte-predominant subtype Hodgkin lymphoma?

PM Nodular lymphocyte-predominant subtype Hodgkin lymphoma is rarely, if ever, associated with EBV. This subtype is a rare form of Hodgkin lymphoma, and it has a different behavior from classic Hodgkin lymphoma, with different marking. The classic Hodgkin lymphoma markers, CD15 and CD30, are not present on the malignant cells of this subtype. In this subtype the malignant cells mark for CD20, suggesting that nodular lymphocyte-predominant disease is histologically different from classic Hodgkin lymphoma. Some of its features are similar to those of low-grade lymphoma, but there are differences between these two diseases as well. Thus, nodular lymphocyte-predominant lymphoma is subclassified as a separate disease, still under the broader classification of Hodgkin lymphoma.

H&O Can you discuss the development of treatment strategies for early-stage Hodgkin lymphoma?

PM The treatment of early-stage Hodgkin lymphoma in the 1970s and a good portion of the 1980s was primarily large-field radiation. Negative radiographic staging predicted for the absence of disease below the diaphragm in approximately 70–75% of cases, and in the other 25–30%

of cases, disease was found with exploratory abdominal surgery and biopsies. Patients often underwent splenectomy and biopsy of abdominal lymph nodes before treatment was devised. The radiation-alone treatment was for the most part for patients who had a negative abdominal exploration for disease below the diaphragm. The reason for using the surgical staging and the large radiation fields was that the standard chemotherapeutic regimen of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) was very toxic. MOPP was associated with a leukemia risk, deep myelosuppression, sterility in men and many women, and severe damage to the bone marrow. Thus, there was not a lot of enthusiasm for its routine use except in the setting of recurrent or advanced disease.

With the development in the 1970s of the doxorubicin, vinblastine, bleomycin, dacarbazine (ABVD) regimen, which is more tolerable than MOPP and does not have the same significant risk, physicians began to gradually incorporate this chemotherapy into earlier stage treatment. By doing so, this therapy eliminated the main reason to undertake staging operations; over time, it has also allowed radiation oncologists to reduce the field size and doses of radiation. These reductions are important because, although large-field radiation is quite successful, with about 80% of patients cured without recurrence, there is a high risk of secondary cancers induced by the malignancy, often appearing 15–30 years or longer after therapy. There is also some risk of late cardiac disease.

In the absence of a staging operation, European researchers have very carefully over time developed prognostic factors to suggest which patients with early-stage disease (stage I or II) might do better or worse with standard treatment. The patients were divided into groups called “favorable” or “unfavorable” early-stage disease. Negative prognostic factors included very bulky chest disease, large numbers of sites of disease, and in one trial, age over 50 years. The European Organization for Research and Treatment of Cancer and the German Hodgkin Study Group have organized trials based on these prognostic factors in stage I and II disease. Notably, almost all these studies in early-stage disease originate in Europe rather than the United States or Canada. Over time, these trials have found that patients with favorable early-stage disease can have a reduction in treatment without compromising the recurrence risk. Therefore, physicians have reduced the standard 6-month regimen of ABVD to 3 or 4 months. There are some trials examining even shorter courses of chemotherapy. Additionally, in this setting it has been possible to reduce the radiation field from a large field to one that covers only the involved nodal region, and radiation doses are now less than they were with radiation alone. Again, trials are under to examine reducing these radiation doses further. In the favorable

early-stage patients, approximately 90% are cured without recurrence. Long-term risk is still being assessed, but from the evidence available, it is expected that the risk will be decreased with these reductions in therapy.

In the favorable early-stage patients, researchers have examined in five different trials the possibility of eliminating the risk from radiation by using chemotherapy alone. Significantly, all the trials show increased recurrence risk with the standard 6 months of chemotherapy as compared to shortened chemotherapy and limited radiation. The magnitude of the increased recurrences is difficult to predict as yet, but there is probably a 20–25% risk of recurrence with chemotherapy alone versus an 8–10% risk with the combination of radiation and a shorter course of chemotherapy. Debate remains about the meaning of the difference in the recurrence rates because survival differences have not yet been seen. Some researchers discount the recurrence risk because of the lack of survival differences whereas others believe that the recurrence differences are significant because with recurrence, the risk of dying from Hodgkin disease increases, and the intensive treatment used in recurrence carries a high risk. The National Comprehensive Cancer Network (NCCN) recommends a standard treatment approach in favorable early-stage patients of somewhat reduced chemotherapy and involved-field radiation. Outside of a clinical trial or special circumstances, the NCCN does not recommend either radiation or chemotherapy alone.

For the unfavorable early-stage patients, there have been some dose-reduction trials that involve lower doses of chemotherapy. Some trials suggest that combined with radiation therapy, 4 months of chemotherapy instead of 6 months is a possible regimen. ABVD has been shown to be more effective than MOPP in this setting. Small-field radiation has shown equivalent results to the large-field approaches. There are data suggesting that in the unfavorable patients, too much reduction in chemotherapy increases the risk of recurrence, whereas this observation is less true for the favorable patients. There are almost no data on chemotherapy alone for the unfavorable patients, but the little data that exist suggest there are very large differences in recurrence rates favoring the combination of chemotherapy and radiation.

H&O What are the risks of secondary malignancy in patients with Hodgkin lymphoma?

PM There are five major types of second tumors that comprise 75% of all secondary cancers. It is important to focus on these tumor types because there is potential for improving on the magnitude of the risk. The five are: other lymphomas, leukemia, gastrointestinal tumors, breast cancer, and lung cancer. There appear to be no

identifiable risk factors for the non-Hodgkin lymphoma (NHL) risk. Patients who develop NHL generally respond well to treatment, but there are no prediction or surveillance strategies for this secondary malignancy. The leukemia risk has decreased significantly with the use of ABVD. Gastrointestinal tumors result mostly from large-field radiation rather than the current approaches. These tumors represent a diffuse group of disease, so it is difficult to identify specific strategies for detecting the tumors earlier.

The two secondary malignancies that warrant the most attention are breast and lung cancers. Breast cancer risk predominates in patients younger than 30 years at the time of treatment and is also present in some women 30–35 years old. There are no data to suggest that there is any risk if a woman is treated after age 35. The risk relates to the amount of the breast in the radiation field. The current, modern treatments rarely treat under the arms, the location of much of the breast tissue when the fields are set up. The risk of breast cancer is probably reduced by lower doses of radiation and smaller fields in comparison to the large mantle fields used in the past. However, more data are needed because the increased breast cancer risk does not appear until 15 years or longer after treatment for Hodgkin lymphoma. For women treated with radiation at a young age, it is recommended that annual mammograms are given beginning 8 years after treatment, which is in advance of when breast cancers are seen. Additionally, a trial is now testing the use of magnetic resonance imaging (MRI) as a more sensitive detection method than mammogram. There is some evidence that tamoxifen administered to women who have undergone radiation therapy for Hodgkin lymphoma may prevent some of the excess breast cancers from occurring. The biggest predictor of lung cancer risk is smoking. The MOPP chemotherapy and radiation therapy confer some risk, but the addition of smoking increases the risk dramatically. It has been calculated that patients who have a smoking history, even prior to treatment for Hodgkin lymphoma, of a pack per day for 10 years or the equivalent (eg, two packs per day for 5 years) have a one in four chance of developing lung cancer in their lifetimes. Screening with computed tomography (CT) has been put into place because in the past, the malignancies were not detected until patients were symptomatic. Chest radiographs are ineffective at detecting the malignancies at an early stage. It is hoped that with screening and detection of early lesions, patients can be cured. In fact, there is some anecdotal evidence of effective treatment and possibly cure in people detected with early screening techniques.

The strategy to prevent secondary cancers has been to reduce treatment as much as possible and then to develop surveillance and prevention strategies to reduce late risks.

It is important to discuss the risks with the patient at the time of initial treatment. For example, in a heavy smoker or a young woman, it is important to discuss the possibility using of chemotherapy alone, which would result in a higher recurrence risk than the combined-modality treatment but would carry a lower breast or lung cancer risk. Physicians must in the end make a recommendation to their patients, however, and polls have shown that different physicians emphasize recurrence or late complications differently. In general, the survival rate in Hodgkin lymphoma is very good, and the median survival after treatment is predicted to be 40 years or greater. We have tried to develop better surveillance, screening, and follow-up techniques for patients, and we recommend continued follow-up over a patient's lifetime.

H&O What is the risk of cardiovascular complications in this setting?

PM Cardiovascular complications do not affect survival the way second tumors do, but increased mortality is seen with cardiac disease, which tends not to be seen until 15 or 20 years after treatment. There are three potential aspects of disease: leakage from the valves, which is generally not significant; an increased risk of coronary vascular disease and heart attacks; and an increased (though not great) risk of arrhythmia. There are ongoing cardiac screening programs for these problems. It has been shown that patients who have other risk factors (eg, hypertension, hypercholesterolemia) are more likely to develop cardiovascular problems after chest irradiation, and prevention strategies exist to identify these patients and tailor therapy by reducing the risks associated with chest irradiation.

H&O What problems are associated with the treatment of elderly patients in this setting?

PM Survival for patients treated at age 50 or older decreases significantly compared to younger patients. Part of the explanation for this decrease is that survival curves are based on mortality from all causes, not just Hodgkin lymphoma; another part relates to the salvage treatment for recurrence in patients over 50 years, which is toxic and not as successful as in younger patients. Treating elderly patients is complicated because aggressive treatment can incur problems but less aggressive treatment can allow recurrence. In general, it is best to avoid recurrence in older patients because they do not do particularly well in that setting. With the data available on strategies to reduce treatment, it is possible to administer both radiation and chemotherapy, reducing the amount of both, in order to reduce the late risk and offer a better chance of cure without recurrence.

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