Treatment of Advanced Hodgkin Lymphoma: The More Things Change, the More They Stay the Same

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As wise people at least as far back as Heraclitus (fifth century BC) have observed, change is the only constant. Change is the vehicle through which we make progress. But progress is not the inevitable product of change. Some changes lead to improvement, some lead to decline, and some produce no perceptible improvement or decline. John F. Kennedy said, "There is nothing more certain and unchanging than uncertainty and change."

The most effective treatment for advanced Hodgkin lymphoma since the 1960s has been combination chemotherapy. The current treatment of choice is a four-drug combination—doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)—that was developed and first reported 37 years ago.

The latest of the new-and-improved treatments to follow this fateful path is Stanford V, a regimen involving doxorubicin, vinblasto-nine (MOPP)2 and ABVD—took this disease from incurable to curable in nearly 75% of patients, an authentic quantum leap in efficacy. However, since then, genuine progress has been ephemeral—here today, gone tomorrow. A new regimen will be developed and touted. Then it will be compared with the standard ABVD and found to be no better.

The latest in this line of treatments is Stanford V, a regimen involving doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, and prednisone. Widely hailed for its brief duration of treatment and apparently high level of activity, Stanford V was elevated to the status of acceptable primary treatment primarily on the basis of phase II data. An initial phase III study comparing Stanford V to ABVD and a 10-drug regimen found that ABVD was superior to Stanford V; however, the Stanford V regimen was not administered in that study as its developers had intended. Modifying a regimen without supporting data seems to be a common affliction in Hodgkin lymphoma clinical trials. The authors’ goal of limiting exposure to radiation therapy because of its late fatal toxic effects was laudable. However, we really do not need more data to convince us that a regimen might not work as well if not administered as intended.

A randomized trial from the United Kingdom compared ABVD with Stanford V. Fewer patients randomly assigned to ABVD received radiation therapy (53% v 73% on Stanford V), but with a median follow-up of 4.3 years, the 5-year progression-free and overall survival rates were not different between the arms. Of course, the rates of late complications cannot be assessed at this early time point.

In the article that accompanies this editorial, Gordon et al report results from a large Intergroup study assessing Stanford V versus ABVD. In this study, ABVD was administered together with radiation therapy only in 41% of patients, primarily those with large mediastinal masses; in contrast, 73% of Stanford V–treated patients received combined-modality therapy. Because of the efficacy of salvage therapy in this disease, failure-free survival was chosen as the primary end point rather than overall survival. The study accrued nearly 800 evaluable patients and is reported with a median follow-up of 6.4 years. Failure-free survival for patients on the ABVD arm was 74%; for patients on Stanford V, failure-free survival was 71%. From the United Kingdom and North American Intergroup studies, it seems safe to conclude that Stanford V does not cure more patients with advanced Hodgkin lymphoma than does ABVD.

The question, then, becomes this: does Stanford V have any advantages over ABVD that would make it a more desirable choice for primary treatment? Stanford V is administered for a shorter duration and provides lower cumulative doses of doxorubicin and bleomycin than does ABVD. By contrast, ABVD does not contain alkylating agents and reduces the need for radiation therapy compared with Stanford V. The presence of both alkylating agents and radiation therapy in the Stanford V regimen is of concern, even though the creators of this regimen hoped that lower doses of both carcinogenic agents would somehow fall below an imaginary threshold for carcinogenicity. We anxiously await long-term follow-up of patients on these two large studies to assess fertility, cardiac and pulmonary complications, and second malignancies. More attention needs to be paid to collecting data on quality of life and late illnesses in patients cured of Hodgkin lymphoma.

The evidence that Stanford V is not an improvement over ABVD answers one major current question in the treatment of advanced Hodgkin lymphoma. Other questions include is radiation therapy needed and if so, who should receive it? Is there a role for midcycle positron emission tomography (PET) scanning in treatment planning and if so, what is it? What about escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); and is there any prospect for new effective therapies that might actually be an improvement over ABVD?

Is Radiation Therapy Needed and If So, Who Should Receive It?

Regardless of whether lower doses and smaller fields reduce radiation late effects, no reduction in exposure can reduce the risk to zero. Current evidence identifies two subsets of patients as benefiting from...
the use of radiation therapy as a component of primary treatment. Patients receiving consolidative radiation therapy after a chemotherapy-induced complete remission do not appear to benefit; but those whose best response to chemotherapy is a partial response appear to have an improved outcome with the addition of involved-field radiation therapy.\(^8\)\(^9\) If the patient has small-volume residual disease after a full course of six cycles of chemotherapy, the addition of involved-field radiation therapy can allow those patients to have survival similar to those who achieved a complete response to chemotherapy alone.\(^3\) Similarly, patients with large mediastinal masses seem to fare better with the addition of involved-field radiation therapy,\(^10\) but randomized trials in which the use of radiation therapy is the only variable have not been conducted. Thus, it would seem reasonable to restrict the use of radiation therapy in primary treatment to the 8% to 10% of patients who do not achieve a complete response with six to eight cycles of ABVD chemotherapy and the 20% to 25% presenting with large mediastinal masses.

**Is There a Role for Midcycle PET Scanning in Treatment Planning and If So, What Is It?**

PET scanning after two cycles of chemotherapy has been shown to be a prognostic factor for relapse in Hodgkin lymphoma.\(^11\)\(^12\) Patients who have negative PET after two cycles of chemotherapy are much less likely to relapse than those who do not. But the midcycle PET scan may not be a strong enough prognostic factor for making treatment decisions. Patients whose PET scans are negative at the completion of therapy seem to do well, whether their interim scans were negative or positive.\(^13\) A substantial fraction of patients with positive PET scans early in treatment (65% in this study) will still be cured by ABVD with or without involved-field radiation therapy. Nevertheless, many investigators have rushed to study the impact of intensifying therapy for patients with PET-positive scans after two cycles of treatment. As those randomized study results are published, we will learn whether exposing all of those patients to more intensive treatment (and the attendant late toxicity) requires changing treatment strategies after only two cycles of therapy. At the moment, the safest course of action is to deliver six cycles of ABVD and then examine the PET scan. If it is positive, one can add involved-field radiation therapy to the persistently positive sites. If it is negative, one can stop treatment.

**What About Escalated BEACOPP?**

The German Hodgkin Study Group pioneered the escalated BEACOPP regimen in maximally tolerated doses, and it has been shown to produce an improvement in failure-free survival and overall survival when compared with cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD\(^14\) and in failure-free survival when compared with ABVD.\(^15\)\(^16\) The vast majority of patients on the German Hodgkin Study Group HD9 study received radiation therapy in addition to eight cycles of chemotherapy.

Escalated BEACOPP has not gained traction outside of Germany for several reasons. First, BEACOPP has substantially greater acute hematoologic toxicity than ABVD. Second, BEACOPP induces infertility in nearly all men and most women who receive it. Third, BEACOPP has a much higher rate of secondary acute leukemia and myelodysplasia than ABVD has. The initial comparison of BEACOPP with COPP/ABVD did not emphasize the large difference in leukemogenesis at least in part because COPP/ABVD contains alkylating agents. Comparing BEACOPP with COPP/ABVD for rates of secondary leukemia would likely not be as starkly disadvantageous a comparison for BEACOPP as comparing BEACOPP with ABVD. Despite the enthusiasm of the German Hodgkin Study Group for escalated BEACOPP, most physicians treating patients with Hodgkin lymphoma had the impression that escalated BEACOPP was overtreating most patients. Escalated BEACOPP might be 6% to 8% better than ABVD, but one was treating 100 patients with toxic therapy to benefit six to eight, and in some cases, the acute treatment-related fatality rate was as high as 6% to 8%.

Recognizing this concern, the German Hodgkin Study Group conducted another study, recently reported,\(^17\) in which the group showed that the outcome from six cycles of escalated BEACOPP was not inferior to eight cycles and was better tolerated. However, a study by Viviani et al\(^16\) put this debate in the proper context. Given that patients who are not cured by their initial therapy are moved to high-dose therapy and autologous hematopoietic stem-cell transplantation, Viviani et al\(^16\) asked the question of whether ABVD or BEACOPP primary treatment leads to more cures when planned high-dose salvage therapy is taken into account. They found that 7-year progression-free survival with primary escalated BEACOPP was 85%, significantly better than the 73% rate with ABVD. However, when taking into account the salvage therapy results, 7-year overall survival was 88% for BEACOPP-treated patients (with treatment failures going to salvage therapy) and 84% for ABVD-treated patients, a difference that was not statistically significant. Rightly or wrongly, this study has been interpreted as supporting an approach in which you cure the 75% of patients who are curable with ABVD and take those not cured to more toxic salvage therapy rather than treat everyone with a much more toxic primary therapy that benefits only a few of them.

**Is There Any Prospect for New Effective Therapies That Might Actually Be an Improvement Over ABVD?**

The explosion in mechanism-based interventions that has had a major influence on the treatment of many types of neoplasms has also provided some promising leads for the treatment of Hodgkin lymphoma. Two agents with novel mechanisms of action have shown quite impressive antitumor effects in patients who have developed progressive disease after salvage high-dose therapy and hematopoietic stem-cell transplantation. Brentuximab vedotin is an immunonconjugate between an anti-CD30 antibody and monomethyl auristatin E, a microtubule inhibitor. The agent induces responses in nearly 75% of heavily pretreated patients with relapsed disease.\(^18\)\(^19\) Its toxicities are fatigue, fever, diarrhea, nausea, neutropenia, and peripheral neuropathy. Its incorporation into a front-line treatment program will need to be completed with special attention to possible overlapping toxicities.

A second class of new agents that seems to have activity in Hodgkin lymphoma is the histone deacetylase inhibitors. These drugs, among other actions, modify chromatin structure and lead to alterations in gene expression that may promote cell death and inhibit angiogenesis. There are four major classes of human histone deacetylases. Mocetinostat is a histone deacetylase inhibitor that has been tested in relapsed Hodgkin lymphoma. It inhibits several of the cell’s histone deacetylases (1, 2, 3, and 11). Disease control rates (response or absence of progression for 6 months) were 24% to 35% for different doses in a phase II trial.\(^20\) Panobinostat is another histone deacetylase inhibitor with activity in Hodgkin lymphoma.\(^21\) Toxicities of these
agents include myelosuppression; thus, incorporation into a primary regimen may be difficult.

There is reason to hope that the next group of changes incorporated into the management of Hodgkin lymphoma will both enhance the fraction of patients cured from between 85% and 90% to between 95% and 100% and decrease the risk of late treatment-related toxicities that can interfere with or shorten the lives of patients who are cured.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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