The Important Role of Secondary Treatment in Hodgkin Lymphoma

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It is time to move on to next key steps of improving recognition of treatment-resistant lymphoma at diagnosis, rather than at treatment failure, by optimally employing biomarkers and improving cure rates by integrating powerful but minimally toxic new systemic agents into primary treatment.

The article “Combined Modality Therapy for Early-Stage Hodgkin Lymphoma: Maintaining High Cure Rates While Minimizing Risks,” by Kelsey and coauthors in this issue of ONCOLOGY, provides a thorough and detailed review of the clinical trial evidence relevant to the choice of optimal treatment for limited-stage Hodgkin lymphoma. The authors document the evidence that this previously fatal neoplasm can almost always be cured. They rightly focus our attention on a key issue remaining to be resolved, namely how to preserve very high cure rates while minimizing major persistent toxicity, which at its worst can prove lethal. Two overview statements can help us focus our attention on this remaining challenge. First, we must remember that today almost all patients with limited-stage Hodgkin lymphoma will be cured, thus in the future these patients will be threatened not by their cancer but by the problems left by its treatment. Second, when addressing a disease that can often be cured with a second course of treatment despite failure of the first course, we must focus on final outcomes such as overall survival and freedom from second treatment failure; we cannot rely on standard progression-free and relapse-free survival, which only address the effectiveness of primary treatment. It is instructive to revisit the evidence summarized by Dr. Kelsey and coauthors with these two key concepts in mind.

With respect to the first core concept, it is obvious that late, potentially severe or even lethal toxicity is caused by the treatments employed. Thus, any unnecessary treatment cannot be justified. Only two of the trials summarized in the article by Dr. Kelsey provide relevant information: the comparison of ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) vs radiation-based treatment described by Meyer et al,[1] and the comparison of COPP-ABV (cyclophosphamide, vincristine [Oncovin], procarbazine, prednisone, doxorubicin, bleomycin, vinblastine) vs COPP-ABV plus radiation described by Wolden and colleagues.[2] All of the other studies employed demonstrably inferior chemotherapy[3-5] or included patients who did not have limited stage disease,[6-8] or both. The two pivotal studies documented excellent long-term overall survival (OS) in the chemotherapy-alone arms: 94% with 12-year OS in the Meyer study[1] and 96% with 10-year OS in the Wolden study.[2] These are the two best long-term OS results ever published for limited-stage Hodgkin lymphoma, and thus provide the benchmark against which any other approaches should be compared. With these unrivalled results achieved in the chemotherapy-alone arms of each of these two most relevant trials, it is obvious that inclusion of radiation for all or even most patients is unnecessary. Dr. Kelsey and his coauthors quite reasonably argue that the late cardiac and second malignancy–associated toxicities of radiation can be expected to be reduced compared with what has been seen following the wider fields or higher doses of radiation used in the more distant past. However, it is unreasonable to anticipate that simply reducing radiation will eliminate all secondary neoplasms. Since inclusion of radiation in the treatment plan for all patients is unnecessary, no radiation-induced secondary neoplasms are acceptable. But, one might object, what about secondary neoplasms and other toxicity contributed by the chemotherapy? Fortunately, the available data are reassuring. As Dr. Kelsey and coauthors nicely point out, all patients with limited-stage Hodgkin lymphoma should receive at least 2 cycles of ABVD. The concern, therefore, is whether there is any further increase in risk associated with adding another 2 to 4 cycles of the chemotherapy. Any such risk must be very small, as is well documented in the cause-of-death analyses from the Meyer[1] and Wolden[2] studies.

One of the most important lessons brought to the field of oncology from the study of Hodgkin lymphoma has been the somewhat unanticipated relevance of the effectiveness of secondary treatment. Stated succinctly, if we have highly effective secondary treatment, we do not need to
cure the disease, regardless of toxicity, with the primary treatment. We must focus on endpoints such as OS or freedom from secondary progression to identify a superior treatment strategy. Limited-stage Hodgkin lymphoma is a case in point. With optimal chemotherapy such as ABVD alone, at least 85% of patients are cured with primary treatment.[1,2] Additionally, quite fortunately, secondary treatment can cure more than half of patients who are not cured with primary chemotherapy, as documented in the Meyer[1] and Wolden[2] reports. These observations allow us to compare overall strategies, instead of just primary treatment results, employing data from those two studies. Thus, a strategy of chemotherapy alone for all plus secondary treatment for the small minority who relapse cures approximately 85% with primary treatment and about 95% overall while risking major late toxicity in only 15% of patients at most. In comparison, giving combined chemotherapy plus radiation to all patients and using secondary treatment for those who relapse means risking major, potentially lethal, late toxicity in 100% of patients, even though no additional patients are cured. Another way to state this comparison is to consider that adding radiation to primary chemotherapy may benefit at most 6% to 7% of patients (85% did not need radiation to be cured and 6% to 10% relapse despite the radiation) but exposes 100% to its toxicity.

Much progress has been made since we discovered we could cure most patients with limited-stage Hodgkin lymphoma. We no longer subject patients to staging lymphangiograms or laparotomies; wide-field radiation has been abandoned; sterilizing regimens such as MOPP (mustargen, vincristine, procarbazine, prednisone) have been replaced by others with little impact on fertility; and mimic diseases no longer mislead hematopathologists and clinicians. To those accomplishments we can now add the seminal observation that radiation is largely unnecessary. It is time to move on to next key steps of improving recognition of treatment-resistant lymphoma at diagnosis, rather than at treatment failure, by optimally employing biomarkers[9] and improving cure rates by integrating powerful but minimally toxic new systemic agents into primary treatment.[10]

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**References:**

**REFERENCES**


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