Despite significant improvements in the treatment of Hodgkin's lymphoma over the past 2 decades, physicians continue to face dilemmas in therapy for the disease, and many cured patients live with complications of treatment. Newer therapeutic options are still needed for the disease, to minimize complications and to improve the treatment of patients in relapse. This review considers the treatment of Hodgkin's lymphoma in younger patients, addressing such issues as which patients with early-stage disease may require radiotherapy, what prognostic factors provide information that can affect treatment choices in patients with advanced disease, and what we have learned about treatment complications in this setting.

We read with interest the article by Dr. Hagemeister, particularly his comments related to the long-term toxicities after therapy for Hodgkin's lymphoma (HL). Clearly, minimizing the long-term toxicity of chemotherapy and radiotherapy is an important goal for improving outcomes, particularly among younger patients and those with limited-stage disease. Because several of the recently reported large retrospective studies of toxicity in long-term survivors of HL include patients who received treatment decades ago, we believe that interpretation of these toxicity data and extrapolation of the data to patients being treated today must be undertaken with caution.

What are the long-term risks?
Two of the largest retrospective reports of long-term toxicity in survivors of HL come from the Netherlands and the United States. The retrospective experience from the Netherlands involved 1,261 patients treated for HL before age 41. Follow-up exceeded 17 years, and 861 patients (68%) were treated from 1965 to 1979.[1] In this series, HL was the primary reason for excess mortality in the first 10 years after therapy, whereas causes other than HL constituted the primary reason for excess mortality after 10 years. Higher relative risks for excess mortality from solid tumors were significantly different based on the time of treatment, with a relative risk of 7.0 to 7.2 observed for patients treated from 1965 to 1979, and a lower relative risk of 4.4 observed for patients treated from 1980 to 1987. This trend likely reflects the emergence of modern radiotherapy techniques. The US series from the Dana-Farber Cancer Institute included 1,319 patients treated from 1969 to 1997, with a median follow-up period of 12 years.[2] A total of 181 second malignancies and 18 third malignancies were observed; the relative risk of second malignancies was significantly higher with increased radiation field size ($P = .03$). By 5 years posttherapy, the relative risk of cardiovascular disease exceeded the risk in the general population. In the US series, the majority of patients treated with combined-modality therapy received wide-volume, extended-field radiotherapy (total nodal, mantle/para-aortic, or pelvic/para-aortic irradiation) rather than the involved field radiotherapy currently employed in HL trials.

Are the risks applicable to patients treated on contemporary protocols?
Results from these large retrospective series raise several issues regarding toxicity of HL therapy. There is no doubt that the toxicities resulting from treatment administered in the past are excessive. However, patients treated in this era typically received MOPP chemotherapy (mechlorethamine [Mustargen], vincristine [Oncovin], procarbazine [Matulane], prednisone), subtotal nodal irradiation (STNI), or some combination of the two. Current chemotherapy regimens such as ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) are clearly less leukemogenic than MOPP. Long-term toxicity of radiotherapy is likely a function of radiation technique, field size, and dose. Historically, doses of radiotherapy were greater than 40 Gy, but doses ranging from 20 to 30 Gy are more typical in the era of combined-modality therapy. The use of large fields is extremely rare now that randomized clinical trials have convincingly demonstrated that involved-field radiotherapy can produce equivalent progression-free survival with less toxicity.[3,4] Emerging data suggest that reductions in field size and dose will result in fewer secondary malignancies.[5] In addition, investigation of further field reductions to "involved lymph node only" fields and tailoring of
radiotherapy fields and doses based on the findings of positron-emission tomography (PET) imaging is likely to result in reduced normal tissue exposure and toxicity.[6]

Should radiation therapy be included in the treatment of limited-stage Hodgkin's lymphoma? The literature is clear that consolidative radiotherapy improves relapse-free survival in HL patients. At least six clinical trials have attempted to answer the question of whether equivalent outcomes could be achieved with the elimination of radiotherapy.[7-12] One relatively small study from Memorial Sloan-Kettering Cancer Center demonstrated that radiotherapy could be safely omitted, but the remaining five trials indicated an increased risk of relapse when radiotherapy was not included. Two of these studies comparing chemotherapy alone with chemotherapy and consolidative radiotherapy (ie, European Organisation for Research and Treatment of Cancer [EORTC]/Group d'Etude des Lymphome d'Adulte [GELA] H9F, Children's Cancer Group [CCG] 5942) required premature closure of the chemotherapy-alone arms due to an unacceptably high number of relapses.[7,8] Current trials (EORTC/GELA H10, Children's Oncology Group [COG] AHOD0431 and AHOD0031) are investigating whether radiation therapy can be eliminated in patients demonstrating an early radiographic response to chemotherapy. However, based upon the current evidence, our practice is to offer combined-modality therapy to all our patients with limited-stage HL. The optimal duration of chemotherapy and dose of radiotherapy is likely a function of individual patient prognostic factors and emerging data from the German Hodgkin's Lymphoma Study Group will help sort out these remaining issues.[13]

Should patients with advanced Hodgkin's lymphoma receive something other than ABVD? Presently, we still consider ABVD to be the standard of care for advanced-stage HL. Certainly there are "issues" with this regimen including the questionable value of dacarbazine, the potential for bleomycin lung toxicity, and the mediocre cure rate in individuals with International Prognostic Scores (IPS) 4 to 7. Fortunately, severe bleomycin lung toxicity is a relatively infrequent event, and patients with IPS 4 to 7 disease comprise less than 25% of the population.[14] Because of the issues with ABVD, attempts to replace this regimen are ongoing.

For IPS low-risk patients, the regimen with the most promise is Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone).[15] An intergroup trial (E2496) comparing Stanford V to ABVD recently completed accrual and will determine whether Stanford V represents a therapeutic improvement in advanced HL. For patients with IPS high-risk disease, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) deserves consideration, as it was associated with improved event-free and overall survival compared to COPP-ABVD in a large randomized clinical trial.[16] In a subsequent subset analysis, the overall survival advantage was limited to patients with an IPS 4 to 7.[17] A current EORTC trial is comparing four courses of escalated BEACOPP followed by four courses of baseline BEACOPP to eight courses of ABVD. In summary, for low-risk patients, Stanford V is a very reasonable option, and for high-risk patients, escalated BEACOPP is a reasonable option. However, until the results of E2496 and the EORTC trial are available, we believe ABVD remains the standard.

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References:


4. Engert A, Schiller C, Josting A, et al: Involved field radiotherapy is equally effective and less toxic compared with extended filed radiotherapy after four cycles of chemotherapy in patients with early
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