Balancing Risks and Benefits of Therapy for Patients with Favorable-Risk Limited-Stage Hodgkin Lymphoma

The Role of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Chemotherapy Alone

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KEYWORDS

• Hodgkin lymphoma • Chemotherapy • Combined modality therapy
• Radiation therapy • Review

KEY POINTS

- More than 80% of patients with stage IA to IIA nonbulky Hodgkin lymphoma are cured with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy alone.
- Death after a diagnosis of Hodgkin lymphoma is more commonly caused by factors unrelated to disease progression and includes treatment-related adverse late effects.
- Follow-up into the third decade after treatment is required to properly assess overall survival after radiation therapy.
- Refinement of early response assessment using positron emission tomography–computed tomography scans may assist individualizing therapy, including defining those who may benefit most from combined modality therapy.

INTRODUCTION

Current controversies in managing patients with Hodgkin lymphoma are a result of uncertainties in balancing the best measures to eradicate the disease while minimizing the risks of long-term adverse effects that are associated with available therapies.

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For patients with localized Hodgkin lymphoma and favorable-risk features, debates relate to the relative merits of treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy alone versus combining fewer cycles of this treatment with localized radiation therapy (RT); for those with advanced disease, debates center around use of ABVD versus bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine (BEACOPP). Common to both debates is realization that most clinical trials that inform practices do not directly address the morbidities and mortality that become apparent in the second and third decades after treatment and that available data about these long-term outcomes relate to previous treatment strategies that are now outdated.

Reviews describing these debates benefit from placing current perspectives onto a background of previous accomplishments in managing patients with Hodgkin lymphoma. Early in the twentieth century, the diagnosis was fatal to all but a few with accessible, localized tumors, in whom radical surgical excision afforded freedom from disease.[1,2] Pioneers in RT discovered means to control localized disease,[3–5] over time observing fewer relapses with increasing radiation fields, leading to adoption of extended-field irradiation encompassing the mantle field (axillary, mediastinal, and axillary nodes), spleen, and para-aortic region.[6,7] Simultaneously, chemotherapy evolved from single-agent nitrogen mustard[8] to combinations resulting in the possibility of cure, even for those with advanced disease.[9] Cure rates increased with coadministration of radiation and chemotherapy, termed combined modality therapy (CMT).[10] By the turn of the millennium, long-term disease control was observed in 80% to 90% of those with favorable limited-stage Hodgkin lymphoma treated with CMT, and many reports described cure rates of greater than 90%.[10–12] With long-term follow-up of young survivors, there was increasing recognition of the problem of late treatment-related toxicities, resulting in premature death, despite cure of Hodgkin lymphoma.[13] Over recent decades, strategies attempting to reduce late effects and maintain or improve disease control in newly diagnosed patients have included adoption of ABVD as the standard chemotherapy regimen because it is more effective than historical regimens and is not associated with the risks of leukemogenesis or gonadal toxicity,[14] reduction of radiation from extended to involved fields,[11] abbreviation of the number of cycles of chemotherapy as part of CMT,[15] and omission of RT by using ABVD chemotherapy alone.[16–18]

The objective of this review is to describe the rationale and context of a treatment decision to use chemotherapy alone as treatment of patients with stage IA and IIA nonbulky Hodgkin lymphoma, building on evidence presented in a recent review.[19] As described in that review, a focus of the current debate about treatment options has been the reporting of the final results of the NCIC Clinical Trials Group (NCIC CTG)–Eastern Cooperative Oncology Group (ECOG) HD.6 trial, in which patients with stage IA and IIA nonbulky Hodgkin lymphoma were randomized to receive 4 to 6 cycles of ABVD alone (the choice of 4 vs 6 cycles was based on disease-control assessment after 2 treatment cycles) or subtotal nodal radiation, given as a single modality to patients younger than 40 years who had no more than 3 nodal sites of disease and an erythrocyte sedimentation rate (ESR) of less than 50, or combined with 2 cycles of ABVD for patients not satisfying these 3 qualifying criteria.[16] The main results of this trial were that chemotherapy alone was associated with superior 12-year overall survival (94% vs 87%; hazard ratio [HR] = 0.50, 95% confidence interval [CI], 0.25–0.99; $P = .04$) but inferior disease control as assessed by 12-year freedom from disease progression (87% vs 92%; HR = 1.91, 95% CI, 0.99–3.69; $P = .05$). Superior overall survival with ABVD alone was because fewer deaths were observed attributed to causes other than Hodgkin lymphoma.