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CLINICAL TRIALS AND OBSERVATIONS

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Protect our children: Hodgkin lymphoma survivors

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In this issue of *Blood*, Giulino-Roth et al discuss the 10-year follow-up of AHOD0031, a Children's Oncology Group trial for intermediate-risk Hodgkin lymphoma (HL), and again underscore the difficult balancing act required to optimize treatment of this disease.[1]

For decades, the mantra for HL trial design has been "maintain cure rates, minimize late effects," especially in the most vulnerable pediatric and young adult populations. The low hanging fruit—splenectomy, nitrogen mustard, and procarbazine—disappeared without a fuss. In contrast, the use of radiation therapy (RT) in children and young adults with HL continues to keep us up at night. Although RT is highly effective at curing patients with HL, it results in late toxicities and premature deaths. Results from the study by Giulino-Roth et al provide another opportunity to examine these tradeoffs and the role of rapid early response in guiding treatment.

AHOD0031 treated 1711 participants age 21 years or younger with 4 cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC). Rapid early responders after 2 cycles with complete remission after 4 cycles were randomly assigned to 21 Gy involved-field RT (IFRT) vs observation, whereas slow early responders were randomly assigned to IFRT vs dexamethasone, etoposide, cisplatin, and cytarabine (DECA × 2) plus IFRT. Ten-year event-free survival (EFS) and overall survival (OS) results continue to show no benefit from IFRT in rapid early responders (EFS, 83.8% vs 82.5%; OS, 97% vs 97.3%) or to DECA in slow early responders.

Unlike contemporary trials, which use positron emission tomography (PET) to assess early response, AHOD0031 determined early response by computed tomography and gallium or PET scan (for later patients). Only 45% of participants met the criteria for random assignment to IFRT or observation. By comparison, in the EORTC H10 trial of PET-adapted therapy for early-stage HL, 81% of patients qualified for random assignment to IFRT or observation.[2] Somewhat surprisingly, in the EORTC H10 trial, those with a favorable HL prognosis gained significant benefit from IFRT (5-year progression-free survival [PFS], 99% vs 87%; hazard ratio [HR], 15.8), whereas those with unfavorable characteristics did not (5-year PFS, 92.1% vs 89.6%; HR, 1.45). Those with a positive interim PET benefited from treatment intensification, a trend also reported in the DECA arm of AHOD0031 in the subset of patients evaluated with PET (10-year EFS, 69.1% vs 50.9%; $P = .16$). Although current methods for assessing interim response are imperfect, existing data (including that from the Giulino-Roth study) suggest that there is no cost to eliminating RT in early responders with an unfavorable HL and improved outcomes with therapy intensification in those with a positive interim PET.

The primary focus of the Giulino-Roth study was the low 10-year cumulative incidence (1.3%) of second malignant neoplasms (SMNs). Of the 17 SMNs, 16 occurred in patients who had received RT and included acute myeloid leukemia (n = 3), non-Hodgkin lymphoma (n = 3), and 11 solid tumors, most commonly papillary thyroid cancers (n = 6). Nine of 11 solid tumors originated in the RT field. The authors acknowledge that 10 years is early with respect to the reported trajectory of SMNs after treatment for HL. A population-based cohort study of teenage and young adult cancer survivors reported 10-year cumulative incidences of second cancers in HL survivors of 0.6% in males and 0.9% in females, numbers strikingly similar to those in the Giulino-Roth study.[3] However, SMNs increased dramatically after 10 years: 3.4% and 16.5% in males and 7.2% and 26.6% in females at 20 years and 35 years, respectively, with the 2 most common SMNs (lung and breast) rarely occurring before 10 years. Females age 10 to 16 years are at highest risk for breast cancer and males treated with chest RT at younger than age 10 years had the highest risk of lung cancer.[4] In another cohort of HL survivors, the risk of solid cancers disappointingly did not decrease in patients treated between 1989 and 2000 compared with 1965 to 1988, despite significant changes in RT fields and doses.[5] Although the Giulino-Roth article does not describe radiation fields in detail, involved fields for the 35% of patients with stage III or IV disease would be relatively extensive. In addition, mediastinal involvement in most patients with early-stage disease would be expected and would require an RT field that included portions of the breasts, lungs, and heart, even with the most sophisticated and modern techniques.

As early as 1970, the dose of RT to treat childhood HL was limited to 15 to 25 Gy in an effort to reduce deleterious effects on growth and musculoskeletal development, but it is not clear that lower doses result in fewer SMNs, as shown in a small series from Stanford.[6] In adults with early-stage HL, 10-year follow-up of the German HD10 and HD11 studies showed no difference in SMNs after 20 Gy vs 30 Gy.[7] Although there was no difference in

PFS between 20 Gy and 30 Gy in patients with a favorable prognosis, the cohort with an unfavorable prognosis (a population similar to that in AHOD0031) had inferior outcomes with 20 Gy. The article by Giulino-Roth et al suggests that lower doses of RT may be associated with different types of cancer; specifically, 6 of the 11 solid tumors were papillary thyroid cancers, a highly curable cancer with a 5-year survival rate of 98.3%.[8] In balancing late effects vs cure, papillary thyroid cancer seems highly preferable to relapsed HL.

In stark contrast to thyroid cancer, all 3 cases of treatment-related AML were fatal and occurred in patients who received ABVE-PC and IFRT. Two patients with available cytogenetics showed an *MLL* locus rearrangement, a finding associated with topoisomerase II inhibitors doxorubicin and etoposide. Despite the low cumulative incidence of 0.2%, the uniform lethality of this complication highlights the continued need to address both the chemotherapy and radiation components when developing new approaches for treating HL.

Continued massaging of traditional therapeutics and technologies is unlikely to have a significant impact on outcomes in HL. Fortunately, a new era in HL treatment may be upon us. Molecular tests, such as that for circulating tumor DNA, may more accurately identify those who need consolidative therapy. Incorporating highly active, novel agents such as brentuximab vedotin, an antibody drug conjugate, or checkpoint inhibitors into earlier lines of therapy is likely to increase the cure rates, hopefully limiting the need for RT and more toxic agents and helping us protect our children.[9,10]

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HEMATOPOIESIS AND STEM CELLS

Comment on Ishii et al, page 1457

FGF-23: a novel actor in stem cell mobilization

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In this issue of *Blood*, Ishii et al[1] identify a novel role for fibroblast growth factor 23 (FGF-23), an osteocyte-derived hormone that regulates phosphate metabolism, in granulocyte colony-stimulating factor (G-CSF)–stimulated mobilization of hematopoietic stem and progenitor cells (HSPCs).

FGF-23 is a hormone secreted by osteoblasts and osteocytes that acts on the kidneys, parathyroid glands, heart, and bone. Now, as reported by Ishii et al, FGF-23 has been shown to play a role in G-CSF–mediated HSPC mobilization. Linkage analysis studies first identified the role of FGF-23 in phosphate wasting disorders.[2] Targeted ablation of FGF-23 demonstrated its role in phosphate and vitamin D metabolism through its actions in the kidney and parathyroid glands.[3] Intact FGF-23 binds with high affinity to a heterodimer of the membrane-bound FGF receptor 1 (FGFR-1) and Klotho proteins, activating canonical FGF-23 signaling.[4]

Noncanonical FGF signaling can also be mediated by other FGFRs independent of Klotho, particularly with extremely high FGF-23 levels, as in chronic kidney disease.[4] A potential role of FGF-23 in hematopoiesis was initially suggested by increased red blood cell counts and elevated erythropoietin levels in mice lacking FGF-23. Consistent with an inhibitory role of FGF-23 in erythropoiesis, injection of FGF-23 in wild-type mice decreased erythropoiesis.[5] Patients with chronic kidney failure have elevated levels of FGF-23, which may contribute to anemia by suppressing production of erythropoietin by the kidneys. However, direct effects of FGF-23 on erythropoiesis have been postulated, since the receptors activated by FGF-23, including FGFR-1, FGFR-3, and FGFR-4 and Klotho, are highly expressed in erythroid cells.[4,5] Together these findings suggested that FGF-23 may contribute to suppression of erythropoiesis. On the other hand, data have shown that erythropoietin stimulates murine and human FGF-23 production not only in cells of the osteoblastic lineage but also in