Comment on Binkley et al, page 2365

NLP Hodgkin lymphoma: can we get away with less?

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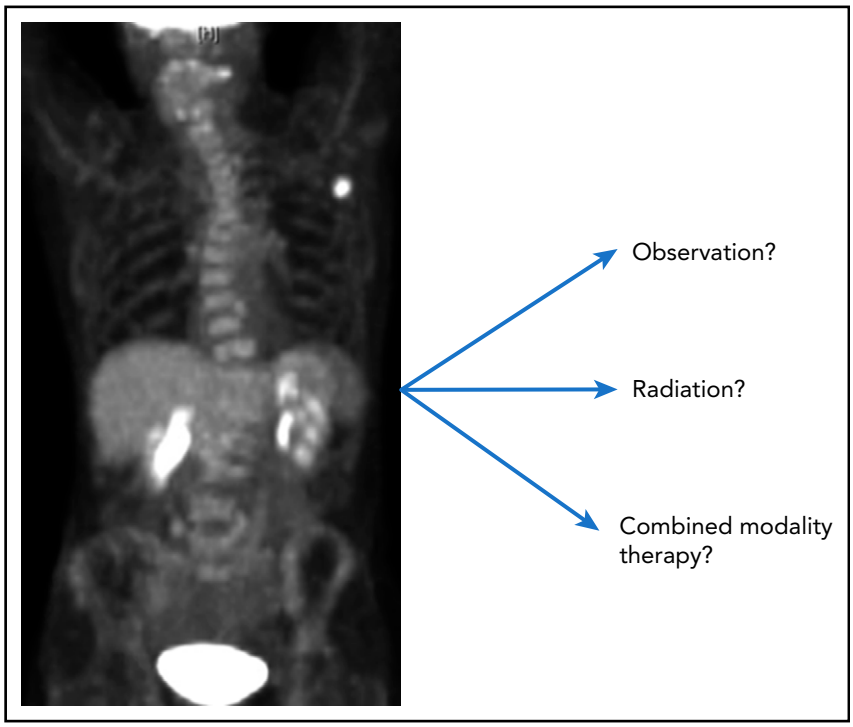
Because of the rarity of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), there are limited data to guide therapy and no single approach to treatment has been agreed upon. In this issue of *Blood*, Binkley et al present a large, multicenter, retrospective series, which provides important insights on treatment patterns and outcomes in NLPHL.[1]

Their analysis includes 559 patients with early-stage NLPHL treated from 1995 through 2018 with either radiation therapy (RT) alone (46%), combined modality therapy (CMT) (32.9%), chemotherapy alone (8.4%), observation (6.6%), rituximab followed by RT (3.4%), or rituximab alone (2.7%). As expected with NLPHL, the outcomes for the patients were excellent, with a 5-year progression-free survival (PFS) of 87.1% and overall survival (OS) of 98.3%. Furthermore, prognosis was good regardless of treatment modality. Among the 2 most common therapies (RT and CMT), there was no significant difference in 5-year PFS (91.1% compared with 90.5%). Because of the inherent bias associated with retrospective analyses, we need to be cautious when comparing treatment modalities. In fact, there were slight differences in patient populations among the treatment modalities, with a higher proportion of favorable-risk patients (by German Hodgkin Study Group [GHSG] criteria) in the RT-only group. However, based upon the highly favorable survival rates in both the RT-only and CMT groups, these data suggest that RT alone may be sufficient for the majority of patients presenting with early-stage NLPHL.

Although it is traditionally treated like classical Hodgkin lymphoma (cHL), NLPHL is characterized by a more favorable course; therefore, many have questioned whether it's necessary to follow the same treatment paradigm used for cHL. This was demonstrated by an analysis from the GHSG that showed improved 50-month survival for patients with NLPHL vs cHL enrolled on prospective GHSG trials.[2] On the basis of these observations, the authors concluded that perhaps NLPHL should be treated with less aggressive approaches. A recent update of their series included 251 patients with early-stage NLPHL followed for a median of 8.8 years.[3] Patients were treated with stage-adapted therapy with RT, CMT, or chemotherapy, and the long-term outcomes were excellent, with 10-year PFS of 79.7% and OS of 93.3%. Importantly, as Binkley et al also noted in their article, only a minority of deaths were related to lymphoma, whereas most were related to second malignancies or nonmalignant conditions possibly related to therapy, thus providing further support for less intense therapy for NLPHL.



Treatment choices for early-stage NLPHL.

An additional important observation from the Binkley et al study was that risk of progression was ongoing as far out as 15 years after initial diagnosis. This raises the question of whether treating early-stage patients with RT changes the natural history of the disease and perhaps indicates that an initial course of observation may be appropriate (see figure). There are limited data regarding the role of active surveillance for early-stage NLPHL. Among 52 pediatric patients with stage IA disease who were observed after complete excision of the disease, a 5-year event-free survival of 77% was reported.[4] In addition, similarly favorable outcomes resulted for the small number of patients in the Binkley et al study who were observed after excision. Borchmann and colleagues[5] recently reported on a series of 37 patients from Memorial Sloan Kettering Cancer Center who were managed with active surveillance among which there were 23 patients with early-stage disease (without complete resection). The 5-year PFS for the early-stage patients initially managed with active surveillance was 65%; however, OS and time to progression after second-line therapy were identical in the surveillance and treatment groups, indicating that there is potentially no drawback from an initial course of observation.

As Binkley et al state in their discussion, "given the excellent survival for patients

with early-stage NLPHL, any risk of late effects with a given treatment must be considered." Thus, a less-is-more approach is warranted for patients with early-stage NLPHL, and prospective studies that evaluate active surveillance are needed. In the meantime, the data suggest that RT alone may be sufficient for most patients with early-stage NLPHL; however, to reduce the risk of any late effect of treatment, observation should be considered.

Conflict-of-interest disclosure: A.J.M. has received research support from Seattle Genetics, Merck, Bristol-Myers Squibb, and Incyte and honoraria from Miragen Therapeutics and Seattle Genetics. ■

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DOI 10.1182/blood.2020005876

HEMATOPOIESIS AND STEM CELLS

Comment on Maia et al, page 2375

Clonal hematopoiesis in myeloma: root of all maladies!

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In this issue of *Blood*, Maia et al investigate the sequelae and clinical significance of dysplastic hematopoiesis at time of diagnosis in patients with multiple myeloma (MM). By performing multidimensional flow cytometry (MFC) to prospectively screen for the presence of myelodysplastic syndrome (MDS)-associated phenotypic alterations (MDS-PA) and clonal hematopoiesis (CH) in bone marrow samples of newly diagnosed MM patients (NDMM), the authors support the use of cost-effective MFC as a screening method to identify dysplasia in patients with NDMM.[1]

As people age, physiologically their tissues accumulate an increasing number of somatic mutations in cancer-associated genes. Although most of these mutations have little or no functional consequences, a mutation may arise and confers a fitness advantage on a cell. In blood, this phenomenon is now recognized as CH and is highly prevalent in the elderly population.[2] Multiple studies have demonstrated that CH is associated with an increased risk of subsequent hematologic malignancies, including acute myeloid leukemia (AML), MDS, myeloproliferative neoplasms, increased risk of cardiovascular events, and adverse outcomes in patients with advanced malignancies.[3,4] Although CH is a hallmark of MDS and leukemias, it may also be found in some individuals who have no detectable hematologic malignancy; in such cases, it is referred to as clonal hematopoiesis of indeterminate potential (CHiP).[5] Increased risk of AML/MDS following therapy has been well documented in MM patients,[6] but whether the genomic alterations driving the myeloid clones are already preexisting at diagnosis or acquired in response to DNA damaging therapy is unclear. In addition, the incidence and clinical significance of subclonal hematopoietic mutations or CHiP in the context of MM remain largely unknown.

In this article, the authors have used MFC to prospectively screen for MDS-PA and CH in the BM of 285 transplant-eligible patients with MM enrolled in the NCT1916252 trial. Of interest, they have found that at diagnosis, and prior to receiving any therapy, 11.6% of MM cases displayed MDS-PA (see figure). Moreover, targeted sequencing of MDS recurrently mutated genes in $CD34^+$ progenitors and dysplastic lineages unveiled CH in half the MM cases with MDS-PA (TET2 and NRAS being the most frequently mutated genes). In contrast, these mutations were identified in only one-fifth of $CD34^+$ progenitor cells in MM patients without MDS-PA. All mutations were subclonal with a median variant allele frequency (VAF) of 8%, marginally but statistically higher, in patients with vs without MDS-PA (9% vs 7%, respectively). Importantly, the authors also reported that the presence of MDS-PA independently conferred a poor survival effect.

How does the presence of MDA-PA or CH affect survival outcomes in MM? How does a higher VAF in nonplasmacytic or nonlymphoid hematopoietic cells negatively impact MM patients' survival as seen in MDS-PA patients? VAF are the result of cell-intrinsic fitness advantages or cell-extrinsic (such as immune or environmental) factors or less likely a mere random effect. Cell fitness is clearly tissue dependent, and therefore, cell-extrinsic mechanisms are considered critical. Independently of the cell-intrinsic parameters, fitness of marrow cell residents also changes over time and could be influenced by changes in the bone marrow niches driven by aging, chemotherapy, immune surveillance, and inflammation.[7,8] Recent studies show that both gene identity and VAF are predictive of progression to AML.[9] In addition, by building a stochastic branching model of hematopoietic stem cell dynamics, Watson et al have recently demonstrated that CH is driven by factors like genetic drift, differences in mutation rate, and cell-intrinsic fitness that become increasable detectable with age.[10] As such, in MM, only studies that longitudinally track individuals over time could distinguish between these scenarios and represent an important area of future work. Along the lines of cell-extrinsic factors, in the current study of CH in MM, Maia et al provide evidence that extrinsic deregulation of immune surveillance with reduced frequency of naive γδ T cells and expansion of CCR7 negative regulatory T cells may be a factor in MM/MDS-PA.