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.

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HEMATOPOIESIS AND STEM CELLS

Comment on Maia et al, page 2375

Clonal hematopoiesis in myeloma: root of all maladies!

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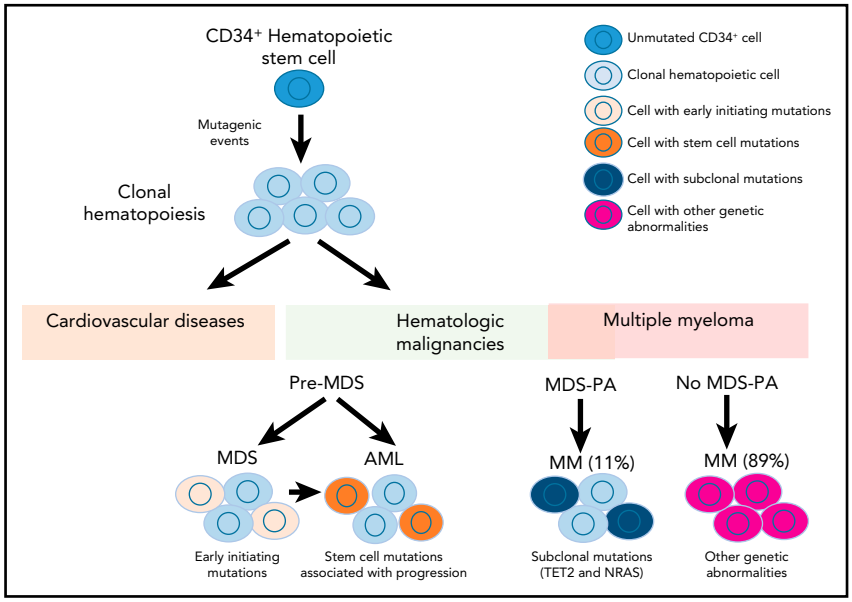
In this issue of *Blood*, Maia et al investigate the sequelae and clinical significance of dysplastic hematopoiesis at time of diagnosis in patients with multiple myeloma (MM). By performing multidimensional flow cytometry (MFC) to prospectively screen for the presence of myelodysplastic syndrome (MDS)-associated 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.



The hypothetical model displaying the phylogenic evolution from clonal hematopoiesis to hematologic malignancies relating to MDS and MM with MDS-PA is displayed here.

Therefore, is it logical to postulate that immune dysfunction with the ensuing loss of immune surveillance is the driver behind the expansion of CH (higher VAF) as well as the worse survival outcomes in MDS-PA MM? Regarding the causal relationship between MDS-PA, CH, and outcome parameters, the authors report that the presence of MDS-PA at diagnosis anticipated greater risk of developing hematological toxicity during treatment and was independently associated with inferior progression-free and overall survival. Intriguingly, however, and despite their association with the risk of development of secondary malignancies (including MDS), they also reported that the use of immunomodulators (IMID)-based maintenance therapy abrogated the negative impact of MDS-PA on MM patients' survival. The well-recognized immune activating effects of IMIDs may indeed explain this apparent controversial finding and warrant further development of targeted immune-based approaches early in the disease course.

Lastly, using immunophenotypic (MFC) and NGS profiling in a small cohort of MM patients, the authors suggest that MDS-PA and associated clonal hematopoietic mutations are mostly present at diagnosis and very infrequently emerge after high-dose therapy and stem cell rescue. As alkylating agents–induced mutational signature is clearly documented in MM, it is imperative to confirm these findings in a larger cohort of patients with prolonged longitudinal follow-up. In addition, although MFC could be used as a screening method to identify MDS-PA in MM patients, novel sequencing technologies (such as single-cell genomics coupled with feature barcoding) of the MM clone and its bone marrow niche will allow a better detection of CH, VAFs, and their interplay with the innate and adaptive immunity and delineate its impact on clonal fitness and evolutionary dynamics. Such deep understanding will finally lead us to unveil whether CH or its associated immune unfitness is at the root of all maladies!

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Matsuzawa-Ishimoto et al, page 2388

Mouse models usher in precision medicine

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In this issue of *Blood*, Matsuzawa-Ishimoto et al report an intestinal organoid-based platform that re-creates genetic susceptibility to T-cell–mediated tissue injury as observed in a mouse model of intestinal graft-versus-host disease (GVHD), providing a roadmap for precision medicine.[1]

GVHD is a severe side effect of allogeneic hematopoietic cell transplantation (allo-HCT). GVHD of the gastrointestinal track (gut-GVHD) has an adverse impact on the outcome of allo-HCT.[2] Alloreactive donor T cells initiate GVHD,