Leukemia insights

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Making Cancer History®

In this month's Leukemia Insights newsletter, written by Kelly Chien, M.D., Danielle Hammond, M.D., and Guillermo Garcia-Manero, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we provide a summary of our approach to CHIP/CCUS and an overview of the Clonal Hematopoiesis and Leukemia Prevention Clinic, which is a part of the MDS Section at the University of Texas MD Anderson Cancer Center. Learn more about our Leukemia program.

Clonal Hematopoiesis

Introduction

As we age, hematopoietic stem cells can sporadically acquire genetic mutations, a phenomenon termed clonal hematopoiesis (CH). This broad description (Figure 1) encompasses the terms clonal hematopoiesis of indeterminate potential (CHIP), where patients have mutations and normal blood counts, and clonal cytopenias of undetermined significance (CCUS), which refers to mutations with a cytopenia (defined as hemoglobin < 10 g/dL, platelets < 100 x 10^9/L, and/or absolute neutrophil count < 1.8 x 10^9/L)[1]. These mutations have been detected in healthy individuals and rise in frequency with increasing age; they are present in the peripheral blood of more than 10% of people ages 65 and older[2,3]. While most of these genetic aberrations are of little consequence, certain changes in the right context can lead to the development of hematologic malignancies, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)[4]. Clonal hematopoiesis is also associated with therapy-related myeloid neoplasms in those who receive cytotoxic therapy for another cancer diagnosis[5,6] and are now a recognized risk factor for and causally implicated in the development of several chronic disease of aging and/or inflammation, especially atherosclerotic cardiovascular disease[7,8]. Furthermore, there have been several population studies linking specific clonal hematopoiesis mutations to environmental exposures, such as smoking and certain antineoplastic agents[9].

Studying clonal hematopoiesis not only provides the opportunity to test early-intervention and prevention strategies for people at the highest risk for developing hematologic malignancies, but also allows for a better understanding of the origins of MDS and related myeloid

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neoplasms. We provide a summary of our approach to CHIP/CCUS and an overview of the Clonal Hematopoiesis and Leukemia Prevention Clinic, which is a part of the MDS Section at the University of Texas MD Anderson Cancer Center.

The MD Anderson Experience with Clonal Hematopoiesis

In the Department of Leukemia at the University of Texas MD Anderson Cancer Center, we evaluated 78 patients with 1 myeloid somatic mutation on next generation sequencing (NGS) from 2015 to 2021. Of those, 46 patients had concurrent cytopenias. As expected from a tertiary cancer center, 76% had a previous cancer diagnosis and 56% had received cytotoxic therapy for another primary malignancy. More than 75% of patients had moderate or severe comorbidities by the ACE-27 score[10,11], with 73% of patients suffering from cardiovascular conditions. A total of 58 patients were observed, and all treated patients had CCUS. Therapies received include growth factors, non-steroid immunosuppressive therapies, corticosteroids, iron supplementation, intravenous immunoglobulin, and rituximab. Twelve patients (15%) transformed to MDS or AML. With a median follow-up time of 27 months, 20 patients (26%) died of various causes including primary malignancy (35%), complications from other comorbidities (20%), MDS/AML (20%), or infections (15%). Therefore, close monitoring of CHIP/CCUS patients for both progression to MDS/AML and extra-hematologic manifestations is paramount.

This retrospective review (pending submission/publication) demonstrates that most individuals with clonal hematopoiesis will not develop a hematologic malignancy in their lifetime. It is of utmost importance to identify the types of clonal hematopoiesis that lead to clonal expansion and malignant progression with the goal of early intervention to prevent malignant transformation.

Clonal Hematopoiesis and Leukemia Prevention at MD Anderson

The increasing frequency with which individuals with clonal hematopoiesis are identified and the growing knowledge about the potential clinical implications of clonal hematopoiesis has led to the recent development of specialized hematologic precursor clinics, including MD Anderson. The aims of our Clonal Hematopoiesis and Leukemia Prevention Clinic are:

1. Natural History Study: to advance our understanding about the natural history of clonal hematopoiesis and the determinants of clonal progression
2. Health Maintenance: to screen and facilitate appropriate specialist care for associated extra-hematologic toxicities and consequences, especially cardiovascular disease
3. Leukemia Prevention: to identify individuals with clonal hematopoiesis at highest risk of progression to hematologic malignancies and offer precision monitoring and prevention strategies

Figure 2 outlines our clinic framework. There is no evidence to support screening the general population for clonal hematopoiesis. We see referrals for clonal hematopoiesis detected in prospective donors for allogeneic stem cell transplantation and in individuals who have undergone sequencing to evaluate for potential inherited cancer predispositions. But the main referral streams are the following:

- Individuals with cytopenias and suspicion of an underlying hematologic malignancy. This includes both healthy individuals and those with non-hematologic tumors experiencing excessive cytopenias in the setting of antineoplastic therapy. A mutation on peripheral blood NGS does not confer the presence of a myeloid neoplasm[12]. On bone marrow evaluation, these patients do not meet diagnostic criteria for a myeloid neoplasm but have myeloid somatic

mutation(s). Comprehensive laboratory and clinical evaluations are critical to exclude more common etiologies for the patient's cytopenias.

- Patients who undergo bone marrow evaluation for an established non-myeloid hematologic cancer, such as chronic lymphocytic leukemia or multiple myeloma, in whom myeloid somatic mutations are discovered.
- Those with non-hematologic cancers, such as solid tumors, who have undergone sequencing. At MD Anderson, matched blood and solid tumor DNA is routinely sequenced in parallel. If clonal hematopoiesis of potential clinical significance is identified, the patient's primary oncologist is notified and invited to refer the patient to Clonal Hematopoiesis and Leukemia Prevention Clinic. Clonal hematopoiesis in non-hematologic cancers has been shown to have adverse clinical outcomes, such as increased risk of hematologic malignancies and shorter survival[13].

We aim to provide an individualized risk assessment of one's clonal hematopoiesis to inform diagnostic and monitoring recommendations. However, there are currently neither evidence-based management guidelines nor established preventative interventions. Individuals are counseled according to their downstream risk profile of future myeloid malignancies, cardiovascular disease, and autoinflammatory disease. The following sections will review our current framework.

Natural History Study

We perform a complete blood count with differential every 3-6 months, with or without a bone marrow evaluation every 6-12 months. All clinic referrals are approached regarding permission for banking of de-identified blood and bone marrow samples for future research. If the patient provides informed consent, we store the blood and bone marrow samples in our tissue bank for scientific investigation in collaboration with basic science researchers in the Department of Leukemia.

Health Maintenance

Cardiovascular Screening

Clonal hematopoiesis is strongly associated with an increased risk of atherosclerotic cardiovascular disease due to the generation of proinflammatory cytokines and endovascular interaction with circulating clonal macrophage progenitor cells[3,7,8]. The use of existing anti-inflammatory therapies is a promising approach for reducing clonal hematopoiesis-related cardiovascular risk, as shown by the CANTOS trial in which a preferential reduction in secondary cardiovascular events was observed in patients with *TET2*-mutated clonal hematopoiesis treated with canakinumab, an anti-IL-1β antibody[14,15]. All patients undergo a baseline echocardiogram (if not already available) and laboratory testing every 6-12 months, including lipid panel, hemoglobin A1c, and thyroid function tests. If the individual has anginal symptoms, urgent cardiology clinic referral is warranted for a stress test or left heart catheterization. However, if the patient has no anginal symptoms, the risk of cardiovascular disease is calculated by the atherosclerotic cardiovascular disease (ASCVD) 10-year score[16], a risk stratification tool validated for those over 40 years of age. In younger patients, a coronary CT angiogram should be considered. Recently, the use of coronary CT scans to calculate the coronary artery calcium (CAC) score has been advocated to add additional risk stratification to the standard ASCVD score[17]. If needed, aspirin 81 mg and an appropriate statin will be initiated.

Mitigation of Autoimmune Conditions

Less is established about the mechanistic link between clonal hematopoiesis and other comorbidities, but there is a growing body of evidence implicating certain forms of clonal hematopoiesis in the development of

inflammatory conditions, such as gout, arthritis, vasculitis, and adult-onset hemophagocytic lymphohistiocytosis. Patients with *TET2* or *IDH1/2*-mutated clonal hematopoiesis may be at an increased risk due to T-cell dysregulation[18]. Additionally, there has been great interest in VEXAS syndrome, a life-threatening autoimmune condition with relapsing polychondritis involving a rare form of clonal hematopoiesis with mutations in the *UBA1* gene[19,20]. Individuals with clonal hematopoiesis and unexplained autoimmune conditions are co-managed with rheumatologists.

Routine Health Maintenance

Similar to the general population, individuals with clonal hematopoiesis should undergo routine cancer screening and vaccinations according to the Centers for Disease Control and Prevention. The table below summarizes the current US Preventive Services Task Force guidelines for cancer screening.

Cancer	Age	Testing
Cervical Cancer	21-29	Pap smear every 3 years
	30-65	HPV ± pap smear every 5 years
Breast Cancer	25-39	Breast exam every 1-3 years
	40-75	Mammogram + breast exam every year
Colon Cancer	45-75	Colonoscopy every 10 years
		Virtual colonoscopy every 5 years
		Stool testing every 1-3 years
Prostate Cancer*	45+	Baseline PSA and DRE
Lung Cancer**	50-80	Low-dose CT chest every year

*optional
**those with 20 pack-year smoking history and currently smoke or have quit within past 15 years

Leukemia Prevention

In addition to the standard hematologic monitoring, as described in our natural history study, we aim to identify individuals at highest risk of evolution to overt myeloid neoplasms. There is no standard approach to risk stratification, though many have published potential high-risk features (variant allele frequency [VAF] cutoffs, cytopenia values, specific mutations)[21]. We identify high-risk patients as those with one or more of the following characteristics:

- Causally attributed cytopenias
- High-risk mutations (e.g. *TP53,* splicing mutations)
- Higher mutation burden (higher VAF and/or multiple mutations)

There are no FDA-approved strategies for the prevention of myeloid neoplasms in the setting of CHIP/CCUS. However, we are currently collaborating with other institutions on early intervention options with clinical trials.
Another critical focus is to identify patients with another primary malignancy who are at a high risk of progression to therapy-related myeloid neoplasms. There have been instances of certain antineoplastic agents leading to the development of therapy-related MDS/AML in particular settings of clonal hematopoiesis[9,22,23]. It is imperative to inform their oncologists to engage in a risk-benefit discussion with these patients about their oncologic therapies and potential therapy modifications.

Figure 1

Definition of terms in clonal hematopoiesis

HSC, hematopoietic stem cell; VAF, variant allele frequency.

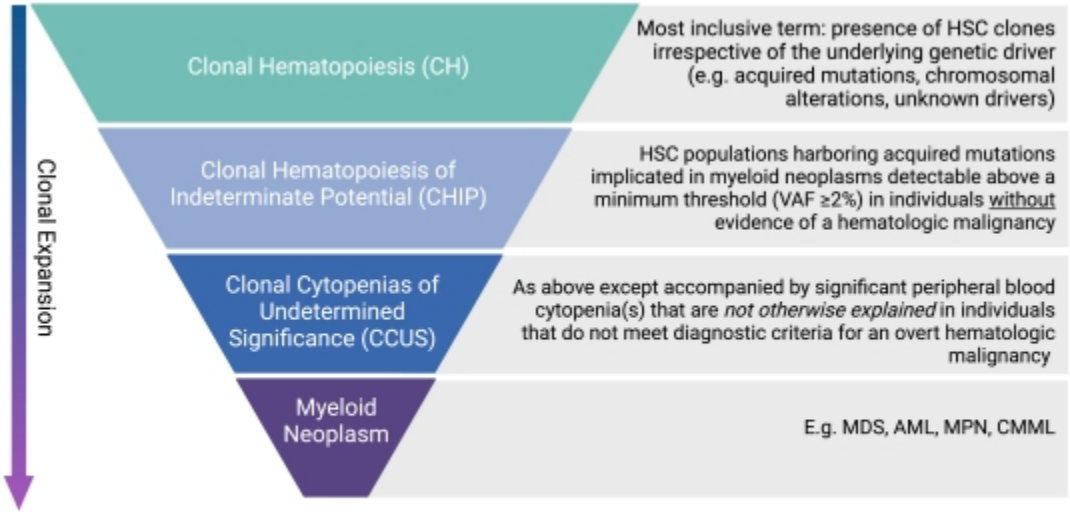
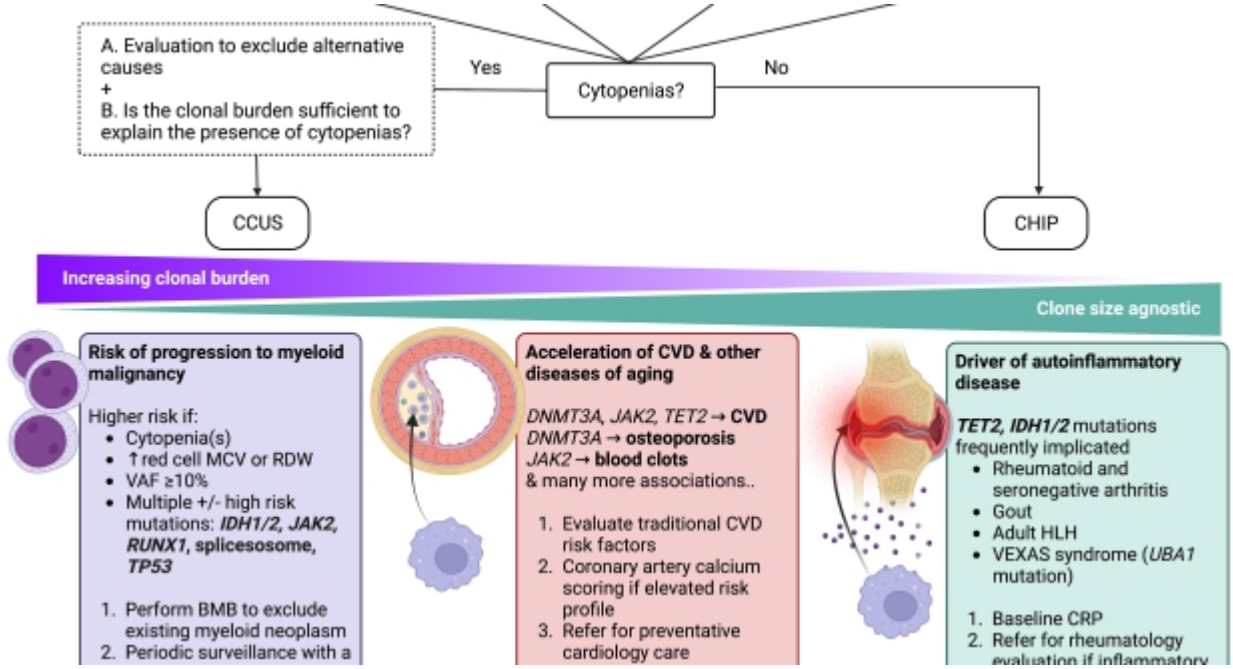


Figure 2

Current clinical approach to clonal hematopoiesis and its downstream implications

BMB, bone marrow; CVD, cardiovascular disease; HLH, hemophagocytic lymphohistiocytosis; VAF, variant allele frequency.



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Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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