Leukemia insights

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Making Cancer History®

In this month's Leukemia Insights newsletter, written by Koichi Takahashi, M.D., Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we summarize some of the recent facts about clonal hematopoiesis (CH) and our clinic dedicated to managing patients with CH. Learn more about our Leukemia program.Learn more about our Leukemia program.

Management of clonal hematopoiesis in cancer patients

Until recently, there has been no practical way for risk prediction and early detection of myeloid malignancies such as acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). However, the discovery of clonal hematopoiesis (CH) as a preleukemic state suggested that early detection, risk prediction, and even prevention of AML/MDS might be possible in the near future. CH is represented by a small population of blood cells carrying at least one driver mutation commonly detected in hematologic malignancies. Here, we summarize some of the recent facts about CH and our clinic dedicated to managing patients with CH.

Definition of CH, CHIP, CCUS

Broadly speaking, hematopoietic cells with evidence of clonal expansion are all defined as clonal hematopoiesis (CH). The clonality of cells can be assessed genetically or phenotypically. The most common way of detecting CH is through DNA sequencing using next-generation sequencing (NGS) technologies, where blood cells sharing the same somatic gene mutations are defined as CH. An overwhelming majority of CH mutations involve genes implicated in myeloid malignancies such as DNMT3A, TET2, and ASXL1. Clonality can also be assessed by chromosome evaluation. CH with recurrent chromosomal abnormalities (e.g., deletion 5q or deletion 7q) has been recognized for many years by practicing physicians and is common in the general population, although less frequent than CH with gene mutations. To distinguish from CH with gene mutations, CH with chromosome alteration is referred to as mosaic chromosomal abnormalities (mCA).

Although the term CHIP (clonal hematopoiesis of indeterminate potential) is often used interchangeably with

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CH, strictly speaking, CHIP is a subtype of CH, where its definition is restricted to CH with gene mutations having greater than 2% variant allele frequency (VAF). This VAF cut-off of 2% was a somewhat arbitrary determination based on the historical sensitivity of conventional NGS. However, since CH with very low VAF is detected in virtually every adult and has little clinical relevance, we will focus our discussion on CHIP here.

Individuals with CH (both gene mutations and mCA) or CHIP should not have any clinical evidence of hematologic abnormalities (i.e. normal blood counts). Patients with CH who are also found to have some degree of cytopenia are diagnosed with clonal cytopenia of unknown significance (CCUS). Individuals with CCUS have a much greater risk of developing hematologic malignancies compared to those with CHIP or CH.

Clinical Impact of CH

The prevalence of CHIP or CH with mCA is a function of age, increasing significantly with each decade of life. The most straightforward clinical consequence of CHIP is that it is associated with an increased risk of hematologic malignancies, especially myeloid neoplasms. The overall relative risk increase is estimated at around 11-fold. However, the risk of leukemic transformation is heterogeneous among CHIP. Some of the high-risk features include CHIP with a VAF greater than or equal to 10%, multiple mutations, and mutations in high-risk genes (e.g. TP53, IDH1/2, spliceosome gene [U2AF1, SRSF2, SF3B1, ZRSR2], DNMT3A R882). Interestingly, early studies found that CHIP is also associated with shorter overall survival and increased risk of atherosclerotic cardiovascular disease (ASCVD) in the general population. Surprisingly, the strength of the association between CH and ASCVD is comparable to well-validated historical cardiovascular risk factors such as high cholesterol, smoking and hypertension. Several preclinical models have revealed the mechanistic basis of this association. CHIP accelerates systemic inflammation via activated monocytes/macrophages and inflammatory cytokines (e.g. IL-1 beta), promoting atherosclerosis. There is an intriguing concept of using the antibody against IL-1b to reduce CHIP-related ASCVD risk, but currently there are no evidence-based interventions.

As a driver of systemic inflammation, CHIP has clinical impacts in addition to ASCVD. Recent studies have found it is associated with a wide variety of conditions, such as graft-versus-host disease (GvHD), immune-mediated toxicities after CAR-T therapy, severe SARS-CoV2 infection, osteoporosis, COPD, and possibly Alzheimer's disease.

CHIP in Cancer Patients

With the increased use of genetic sequencing in oncology management (e.g. liquid biopsy, matched tumor-blood sequencing), incidental discovery of CHIP is becoming frequent in cancer patients. Although there is no study with head-to-head comparison, it appears that CHIP is more prevalent in cancer patients compared to the general population, with approximately 30% harboring CHIP mutations in their blood. Mutational spectrum is also different in cancer patients, with higher prevalence of mutations in DNA damage response genes (e.g., TP53, PPM1D, CHEK2, and SRCAP). This is likely caused by the selection of these mutants under DNA damaging chemotherapy or radiation therapy. In addition, shared risk factors between cancer and CHIP, such as smoking, may account for the increased prevalence of CH. CHIP is detected in cancer patients in several scenarios:

1. CH can be discovered incidentally during germline testing for patients suspected to have familial predispositions to cancer.
2. Tumor sequencing is often accompanied by blood sequencing as a matched control, and CHIP can be uncovered from the analysis of

the blood sequencing data.
3. In the setting of cell-free DNA testing (i.e. liquid biopsy), CHIP can confound the sequencing data.
4. CHIP can be detected on solid tumor sequencing due to blood contamination of tumor samples, leading to false-positive tumor somatic mutation calls.
5. CH can be identified during the evaluation of unexplained cytopenias, often accompanied by bone marrow analysis.

Therefore, the identification of CHIP in cancer patients is an increasing reality for practicing medical oncologists. Furthermore, given its broad clinical implication (e.g. risk of leukemic transformation, ASCVD risk, immune-related toxicities), it has become an important problem for cancer survivorship.

CHIP Clinic and Care Recommendation

In order to meet the demand of professional consultation for the incidental discovery of CHIP, major cancer centers, including our institution, have launched CHIP clinics (here managed by Drs. Koichi Takahashi, Guillermo Garcia-Manero and Courtney DiNardo). There is no standard of care for the management and monitoring of these patients. In the absence of evidence-based guidelines, our clinic offers general management strategies for patients with cancer who have CHIP. First, upon identifying CHIP, we discuss with the primary oncologist whether consultation to CHIP clinic is indicated. In some cases, consultation is not recommended when the patient's prognosis is poor from primary cancer. If indicated, we discuss with the patient the findings and their clinical implications. When patients with CHIP have clinical signs of occult hematologic disease (e.g. abnormal blood counts) and/or high-risk mutational characteristics, such as a VAF greater than or equal to 10% or multiple mutations, consideration for further workup including bone marrow biopsy or aspiration is discussed. Since cancer patients can have various reasons to develop abnormal blood counts (e.g. anemia of chronic illness, infection, chemotherapy-induced cytopenias), it is important to carefully evaluate the relationship between CHIP and the abnormality in blood counts. If no alternative etiology for cytopenias is identified on initial workup, collecting a bone marrow biopsy specimen may be warranted to evaluate for an underlying hematologic neoplasm. Infrequent follow-up, including periodic monitoring of CBC counts, is recommended for patients who have no overt evidence of hematologic disease.

One of the frequent questions from primary oncologists is the risk of therapy-related myeloid neoplasms and whether to change the treatment plans for primary cancer. At this point, we do not recommend changing treatment based on CHIP findings. Although the idea to use CHIP as an independent clinical decision-making tool is tempting, the evidence is not currently sufficient to recommend such a management approach. There is an incomplete understanding of the risk of therapy-related myeloid neoplasms with CHIP, and the risk of compromising the treatment for primary cancer might be more significant. As the risk and time-course for transformation from CH to overt hematologic disease are better characterized, molecular and clinical features may be used to inform treatment planning.

We recommend repeating CBC counts every 3 to 12 months, depending on the progression rate of patients with and without blood count abnormalities. In patients with progressive blood count abnormalities or other symptoms concerning evolving hematologic disease, repeated mutational testing combined with repeated bone marrow biopsy should be considered. Importantly, because of the increased risk of ASCVD, we recommend consultation with cardiologists or primary care physicians to maximize the treatment for modifiable risk factors.

Summary

Incidental findings of CHIP increasingly are becoming common in oncology practice. While evidence-based guidance is lacking, it is essential to refer those patients to the CHIP clinic for optimal management of related risks and potential investigation of occult hematologic malignancies. At the MD Anderson Department of Leukemia, we accept consultation for the management of CHIP. Please feel free to reach out and seek advice (ktakahashi@mdanderson.org).

Announcements

Bridging Oncology and Primary Care Education Series
MD Anderson Cancer Center is featuring an online educational series for all health care provider specialties. This series will feature specialized presentations covering: Gastroenterology, Internal Medicine, Dermatology/Melanoma, Hematology, Breast, Gynecologic Oncology, Immunology, Thoracic and Head & Neck, COVID Related Topics and Hot Topics. The modules are pre-recorded and will be available through July 15, 2021–February 1, 2022. To view more details or register, go to http://mdanderson.org/ccc21.

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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