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Clonal Hematopoiesis and therapy related MDS/AML

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ABSTRACT

Clonal Hematopoiesis is defined as the presence of mutations in peripheral blood in the absence of myeloid malignancies and is thought to occur as a normal part of ageing due to the fitness advantage conferred by these mutations in an ageing hematopoietic compartment. Therapy related myeloid neoplasms are malignancies that occur after exposure to chemotherapy/radiation and are associated with poor survival. Clonal hematopoiesis mutations represent a pre malignant state that can be triggered by exposure to cytotoxic damage and rapid hematopoietic stem cell expansion. We discuss in this review clinical evidence of association of clonal hematopoiesis with risk of therapy related myeloid neoplasms, the underlying mechanisms of clonal expansion under different cellular stresses and recommendations on clinical follow up of patients with clonal hematopoiesis including possible strategies for prevention of therapy related myeloid neoplasms.

1. Introduction

Clonal Hematopoiesis (CH) has been defined as the expansion of one lineage of cells, a clone, at a rate disproportionate to other clones [1]. Evidence of CH was first described in studies of X linked inactivation in women that demonstrated skewing of hematopoiesis with age. In these experiments, imbalanced expression of polymorphic X-linked genes resulting from non-random X inactivation suggested clonally restricted hematopoiesis [2–5]. Subsequently, *TET2* mutations were described in women with X linked skewing in the peripheral blood [6]. More conclusive evidence of CH has been demonstrated in several seminal population-based studies which established that CH is relatively common in healthy populations and increases with age [7–9]. CH mutations are thought to occur in Ln- CD34 +CD38-cells [10] as a result of selection of hematopoietic stem cells (HSC) with increased fitness and proliferative capacity. The occurrence of such mutations is statistically very likely because hematopoietic cells are in a state of constant cell division. Deeper sequencing suggests that at very low allele frequencies, the occurrence of CH is bordering on ubiquitous [11]. The likelihood of clonal advantage increases with age as HSC self-renewal capacity decreases and certain clonal mutations are more fit to expand and contribute to CH [1]. Indeed, the majority of CH point mutations observed in studies to date have been C > T transition mutations, a hallmark of aging-associated change [7–9,12,13].

Population-based next-generation sequencing studies have estimated that CH is detectable in up to 30% of subjects over 60 years old and its presence has been linked to increased risk of hematological malignancies [7–9,13,14]and cardiovascular mortality [7]. CH has also been associated with smoking and an increased red cell distribution width (RDW). The term CH has been interchangeably used with 'Age Related Clonal Hematopoiesis' (ARCH) and 'Clonal Hematopoiesis of Indeterminate Potential' (CHIP). However, while CH generally includes any clonal expansion, without reference to methodology or quantitation, CHIP more specifically refers to the presence of clonal mutations in the peripheral blood at a variant allele frequency (VAF) of at least 2%, in the absence of any known

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cytopenias or hematological disorder [15,16]. This cut off was based on earlier studies and subject to change as data evolves on gene specific risks. CH is the subject of intensive ongoing research and there is a global effort by many groups to establish the timing, pattern, and VAF thresholds of mutation-specific risks and their association with clinical outcomes.

2. CH and risk of AML in normal healthy populations

The presence of a premalignant state up to a decade before the diagnosis of acute myeloid leukemia has been established recently [13,14]. In a study by Desai et al., the authors performed deep sequencing on 212 cases of AML and 212 matched controls without any myeloid malignancy and found that clonal mutations could be demonstrated a median of 9.8 years before the diagnosis of AML [13]. Furthermore, AML cases were four times more likely to have CH at baseline, compared to controls (70% vs. 30%, OR 4, 95% C.I. 2.5–6.3). Although it was previously known that CH is associated with the development of hematologic malignancies, this work was among the first to define mutation-specific risk for the development of AML. Mutations in *TP53* (OR 47.2, 95% C.I. 2.5–879.1), *IDH* (including *IDH1* and *IDH2*) (OR 28.5, 95% C.I. 1.4–562.8), spliceosome genes (including *SF3B1*, *SRSF2* and *U2AF1*) (OR 7.4, 95% C.I. 1.7–32.2), *TET2* (OR 5.8, 95% C.I. 2.6–12.9), and *DNMT3A* (OR 2.6, 95% C.I. 1.5–4.5) were associated with significantly increased odds of developing AML relative to controls. The presence of any mutation was associated with a shorter time to AML among cases (11.9 years vs. 8.2 years after baseline assessment $P < 0.001$). Finally, the VAF of mutations generally increased in serial samples prior to the diagnosis of AML, while this pattern was not observed in age-matched controls with detectable mutations. A simultaneous study by Abelson et al. showed similar results [14]. While screening for AML is not yet practical on a population level, the studies by Desai et al. and Abelson et al. suggest the potential feasibility of identification, screening, and eventually disease interception strategies for patients at high risk for the development of AML.

3. CH and radiation exposure

Some of the earliest indirect evidence of CH comes from observational data derived from atomic bomb survivors. Yoshida et al. observed peripheral blood monocytosis in atomic bomb survivors compared to non-exposed individuals and that the effect was stronger in current smokers [17]. Monocyte levels were increased in both male and female survivors over 60 years old and were associated with increased all-cause mortality. Interestingly, the presence of *TET2* and *DNMT3A* mutations in mouse models is associated with abnormal macrophages and increased atherosclerotic plaque formation, along with evidence of an inflammatory state [18]. Additional data from atomic bomb survivors also supported the presence of an inflammatory state, as evidenced by increased ESR, CRP, and IL6 levels [19–21]. These data provide indirect evidence that CH may be accelerated by radiation exposure. It should be noted that Yoshida et al. excluded survivors with an eventual diagnosis of hematological malignancies from their study to avoid confounding blood monocyte levels with a diagnosis of hematological malignancy [17].

CH in patients with solid tumors has been associated with prior radiation exposure [12] and had the highest co-occurrence in patients with thyroid cancer (37%) [22]. Radioactive iodine is commonly used in treatment of thyroid cancer and although epidemiological studies have shown mixed results with regards to association of RAI with secondary MDS/AML [23–26], a more recent meta-analysis showed that there is a 2.5 fold increased risk of t MN in patients exposed to RAI [27]. Boucai et al. found that in 309 patients with thyroid cancer, the occurrence of CH and CH-PD (presumed driver mutations) increases as the dose of RAI increased with 2–4% increase in odds of CH and CH-PD respectively with every 10 mCi increase in RAI dose. The prevalence of CH in patients with medullary thyroid cancer, which is generally not treated with RAI, was 23% while the overall prevalence in thyroid cancer was 37% [22]. Due to the relatively short follow up period, there was only one t AML that was diagnosed in this cohort, hence making direct association of RAI, CH and t AML not possible.

4. CH and therapy related myeloid neoplasms (t-MN)

Therapy-related myeloid neoplasms (t-MN) are a devastating complication of cancer treatment associated with treatment resistance and poor overall survival [28–32]. As the general population ages, cancer incidence increases, and cancer outcomes improve, there is a growing population of patients exposed to chemotherapy and radiation. Thus, the incidence of t-MN is also increasing and strategies to identify patient-specific risk factors are needed.

Evidence of CH as a risk factor for t-MN initially came from two case-control studies [33,34] (Table 1). Takahasi et al. compared 14 t-MN cases with 54 age-matched controls with lymphoma, with a follow up time of at least 5 years. Peripheral blood was available in these patients at the time of their primary malignancy diagnosis, before the start of chemotherapy [33]. CH with driver mutations was detected in 71% of patients in the case group who eventually developed t-MN, compared 31% of controls ($P = 0.008$). The cumulative incidence of t-MN in patients with and without CH with driver mutations was 30% vs. 7% ($P = 0.01$). The authors also evaluated an external cohort of lymphoma patients treated with CHOP chemotherapy and found similar results, with the cumulative incidence of t-MN at 10 years follow-up of 29% in patients with CH vs. 0% in patients without CH ($P = 0.009$). The effect of VAF on risk of t-MN was not clear in this study with contradicting results in the two cohorts. *RUNX1*, *TP53*, *SRSF2* and *TET2* mutations were more commonly seen in patients who developed t-MN, compared to those who did not.

A similar study by Gillis et al. of 14 t-MN cases and 56 matched controls who had chemotherapy exposure but did not develop t MN, demonstrated that cases of t-MN were more likely to harbor CH compared to controls (62% vs. 27%, OR 5.75, p value 0.01) [34]. About half of the patients with CH had samples taken at baseline before chemotherapy and, interestingly, there was no difference in VAFs for CH in patients when the blood was taken before or after chemotherapy, suggesting that these mutations are likely present

Table 1
Clinical data from studies evaluating risk of t-MN with the presence of CH mutations prior to onset of t-MN. C.I.: Confidence Interval; ASCT: Autologous stem cell transplant; NHL: Non Hodgkin's Lymphoma.

	Study design	Prevalence of CH	CH and t-MN risk	CH associations
Gillis et al. [34]	Case control: 13 t-MN cases and 56 age matched controls (chemotherapy exposure but no t MN)	Overall: 33% t-MN cases: 62% Controls: 27%	Odds of t-MN with CH: 5.75 (95% C.I. 1.52–25.09) PPV of CH: 34.8% (95% C.I. 16.4–57.3) NPV of CH (95% C.I. 76.4–96.4)	CH mutations expanded in 4/6 patients up to diagnosis of t-MN while they decreased in 2/6 patients No difference noted in *TP53* CH prevalence between cases and controls
Takahashi et al. [33]	Case Control: 14 cases of t = MN and 54 controls External cohort, observational: 74 patients with lymphoma treated with chemotherapy	t-MN cases: 71% Controls: 31% External cohort: t-MN cases: 80% No t-MN: 16%	HR of t-MN with CH: 13.7 (95% C.I. 1.7–108) 10 year cumulative incidence: 30% vs. 7% (CH vs. no CH) for case control study 10 year cumulative incidence: 29% vs. 0% (CH vs. no CH) for observational external cohort	71% of mutations present in t-MN samples were detected as CH mutations at baseline prior to chemotherapy exposure *RUNX1, TP53, SRSF2 and TET2* more commonly seen in patients who eventually developed t-MN
Coombs et al. [12]	Observational: 8810 patients with advanced solid tumors	25% overall 4.5% for driver mutations	18 month cumulative incidence: 1% vs. 0.3% (CH vs. no CH) 18 month cumulative incidence for driver mutations: 3.2% vs. 0.35% (CH vs. no CH)	Age, smoking, thyroid cancer, monocytosis, neutrophilic leucocytosis, elevated MCV. PPM1D and TP53 associated with previous chemotherapy/radiation
Gibson et al. [65]	Observational: Cohort 1: 12 patients with t-MN Cohort 2: 401 patients who underwent ASCT for NHL	Cohort 1: 6/12 patients had mutations present in t-MN that were also present prior to ASCT Cohort 2: 29.9% pre ASCT prevalence	10 year cumulative incidence: CH 14.1% vs. no CH 4.3% 10 year cumulative incidence for > 1 CH mutations 25.3% vs. 9.9% for 1 CH mutation	CH associated with worse all cause mortality OS was worse for *PPM1D* mutations compared to presence of other CH mutations (20.8% vs. 39.9% at 10 years)

before chemotherapy and eventually contribute to t-MN after exposure to cytotoxic stress. The positive predictive value and negative predictive value of CH with regard to development of t MN was 34.8% and 89.1% respectively. When matched t-MN and CH samples prior to development of t-MN were available, the authors found that CH mutations in 4/6 patients had expanded to contribute to the t-MN clone, but the other mutations were present in very small VAFs, or even absent at the time of t-MN.

While the two studies above included patients with both lymphoid and solid malignancies, Coombs et al. found that the prevalence of CH in patients with advanced solid tumors was 25% and associated with prior exposure to chemotherapy, radiation, and smoking [12]. The most common mutations observed were *DNMT3A, TET2, PPM1D, ASXL1, ATM,* and *TP53*. As expected, *PPM1D* and *TP53* were commonly seen in patients who were exposed to either chemotherapy and/or radiation. The presence of CH was also associated with increased mean corpuscular volume (MCV), absolute monocytosis, and elevated neutrophils. CH was most prevalent in patients with thyroid cancer, likely due to radioactive iodine (RAI) exposure. Interestingly, monocytosis has also been reported on long-term follow-up of atomic bomb survivors in Japan [17]. In the Coombs study, t-MN was seen in 1% of patients with CH compared to 0.3% in patients without CH at 18 month follow up ($p = 0.003$). When only CH with driver mutations was taken into account, the cumulative incidence of t-MN at 18 months was 3.2% vs. 0.3% in patients with and without CH with driver mutations, respectively ($p < 0.001$). Importantly, the presence of CH in this heavily treated population with advanced solid tumors was also associated with increased mortality from progression of the primary tumor. While the mechanism of this relationship is unknown, it is hypothesized that the effect could be explained by cell to cell interactions between CH cells and tumor cells, leading to alterations in the tumor microenvironment [35]. Also, the use of granulocyte colony stimulating factor (GCSF) in patients with solid tumors has been linked to increased risk of t-MN [36,37]. While there is no data to explain this observation, it is possible that patients who have CH drive this effect and the rapid HSC proliferation induced by GCSF use increases the penetrance of CH clones eventually paving the way for increased risk of t-MN [33].

5. Clonal dynamics of CH mutations prior to diagnosis of t MN

The selection of clones that ultimately reconstitute hematopoiesis may be different based on the type of chemotherapy used [38,39]. It is also possible that chemotherapy induces new mutations, rather than facilitating expansion of preexisting age-related CH mutations (Fig. 1). The incidence and clonal complexity of CH is reportedly higher in patients receiving chemotherapy, compared to those with a malignancy but not exposed to chemotherapy [38]. But, it is important to note that the presence of CH is not an absolute risk for t-MN and the mutations present at the time of detection of CH do not necessarily comprise the clones ultimately identified as part of the t-MN. Some CH mutations may actually decrease in VAF at the time of t-MN diagnosis, making the monitoring of specific CH genes a challenge. Most studies to date have only measured VAF at one time point after chemotherapy, and data on longitudinal changes in VAF prior to the diagnosis of t-MN are lacking. Arends et al. studied clonal dynamics in 72 chemotherapy-treated patients and found that 13/32 (40%) clonal mutations showed a change in VAF by 50% over time [40]. *DNMT3A* clones generally remained stable over time, while clones harboring *RAD21*, *PPM1D*, and *EZH2* mutations increased in VAF, and *SF3B1*, *JAK2*, and *CBLB* clones decreased over time. Certain clones present in the same patient demonstrated differential growth or attrition over time, suggesting that CH may be oligoclonal. Unfortunately, no t-MN cases were reported in this study in the short follow up time.

5.1. TP53 in t-MN

TP53 mutations are present in 23% of t-AML and up to 50% in patients with a complex karyotype and copy number alterations in chromosome 5, 7, 17 [30,32,41–45]. The *TP53* mutations present in CH as well as t-MN are generally in the DNA binding domain [46]. There could be two mechanisms by which *TP53* mutations occur in t-MN: either *TP53* clones are present in patients before the onset of chemotherapy or the chemotherapy itself induces DNA damage, causing *TP53* mutations to arise. Wong et al. demonstrated that both mutational burden, as well as the number of sub clones was similar in *de novo* versus t-AML [39]. Moreover, *TP53* mutations have been detected in normal healthy populations with no exposure to chemotherapy [7–9]. Even in patients with *TP53* mutated t-MN, CH clones with *TP53* mutations have been detected at small VAFs prior to exposure to chemotherapy in the majority of cases [34]. It is unclear whether the inability to detect *TP53* clones prior to chemotherapy in some cases is due to their absence, or rather reflects the detection limits of available testing. Regardless, there is ample evidence that mutant *TP53* clones are frequently present in patients prior to the administration of chemotherapy. These clones are generally resistant to chemotherapy and, thus, have selective advantage in the post-chemotherapy state [38,39]. This escape mechanism is similar to what has been observed in Shwachman Diamond Syndrome (SDS), in which evolution of a *TP53* clone occurs even in the absence of chemotherapy or radiation [47,48]. SDS leads to a stressed state of ribosomal biogenesis that is known to induce p53 expression and lead to growth arrest. Mutated *TP53* clones escape this stress and eventually lead to increased risk of MDS/AML that is biologically similar to t-MN with complex karyotype and TP53 mutations.

The mechanism of progression of *TP53* CH to t-MN likely involves copy number alterations, as patients with *TP53* mutated AML/MDS do not typically present with only single nucleotide variants [46]. Deeper sequencing of CH mutations with *TP53* have demonstrated sub-clonal chromosome 5 and 7 copy number variations years before the diagnosis of t-MN, suggesting that *TP53* clones precede the development of cytogenetic abnormalities in t-MN. It is also important to note that *TP53* CH is known to expand over time and progresses to t-MN such that it forms the bulk of the malignant clone at diagnosis. Such expansion can take place with or without the presence of known risks, such as chemotherapy or radiation [13,14]. In the setting of hematopoietic stem cell transplantation, mutant *TP53* clones are not known to have any specific growth advantage after transplantation induced stress [38].

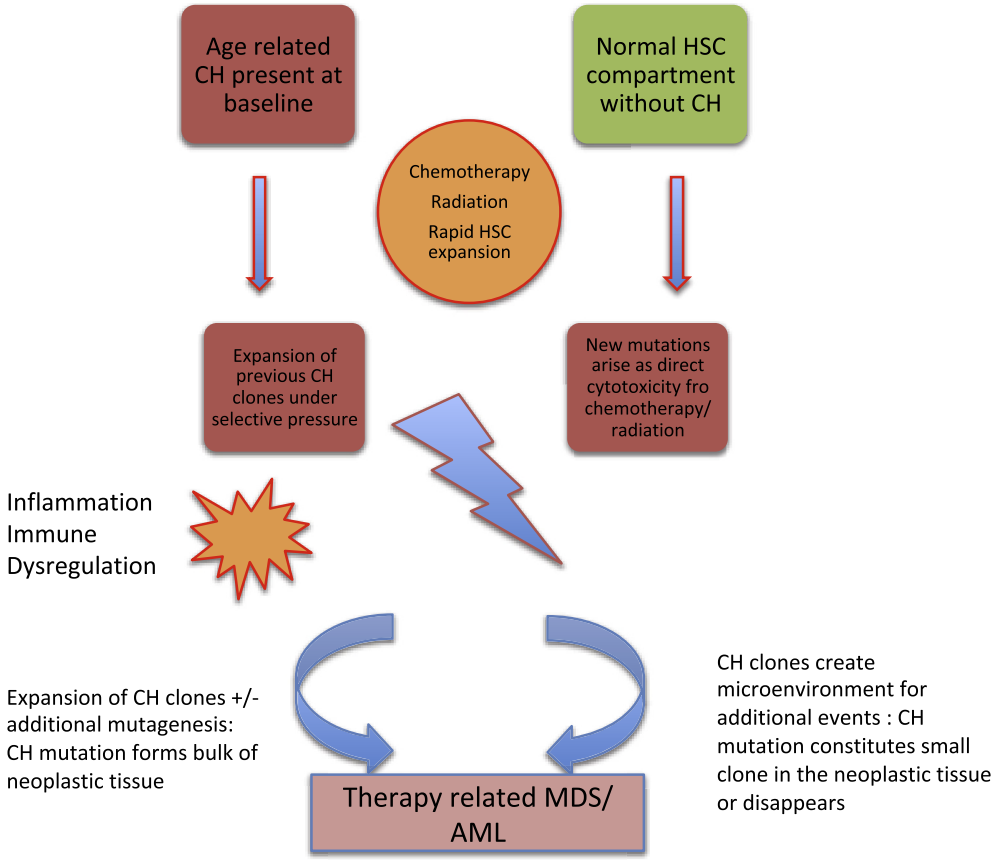

Fig. 1. Putative pathogenesis of t-MN. Expansion of CH clones can be postulated to occur in two ways. Cytotoxic chemotherapy or transplant related stress might lead to rapid expansion of previously present age related CH mutations. It is also possible that new mutations arise due to direct effect of cytotoxic chemotherapy after exposure to the same. Additional steps in mutagenesis usually needed to transform to t-MN. This may be influenced by cell intrinsic and extrinsic factors including immune deregulation, inflammation or stochastic drift. Some CH clones are known to expand and make bulk of the tumor population, thus directly acquiring additional steps in mutagenesis while other CH clones are known to remain stable or disappear giving way to new mutant clones. Such clones promote mutagenesis through other mechanisms that are not completely understood.

5.2. PPM1D and t-MN

PPM1D mutations have been recently reported to be present in 20% of t-MN cases and rarely in *de novo* AML [49]. The prevalence of *PPM1D* CH in chemotherapy treated patients ranged from 2 to 18%, while its prevalence in unselected populations was estimated to be 0.5–5% [50]. Interestingly, unlike *TP53* mutations, *PPM1D* mutations are not associated with a complex karyotype or abnormalities in chromosomes 5 or 7, thus suggesting a different mechanism of leukemogenesis. Unlike *TP53* mutations, *PPM1D* mutations are associated with exposure to specific chemotherapeutic agents, such as platinum, etoposide, cytarabine, and doxorubicin; and there is no association with radiation exposure [12,49]. *PPM1D* mutations are thought to confer resistance to apoptosis via a regulatory feedback loop with p53, leading to inhibition of p53 mediated apoptosis [51,52]. All *PPM1D* mutations seen in both CH and t-MN involve truncating mutations in exon 6 that lead to overexpression of the mutant protein.

PPM1D CH mutations have been observed in peripheral blood samples of patients before and after chemotherapy exposure [12,38,53,54], as well as in the absence of chemotherapy, albeit rarely [9]. It is possible that, like *TP53* mutations, *PPM1D* CH mutations are present prior to chemotherapy in small clones and exposure to specific treatments selects for expansion of these clones. It is also possible that in some patients, exposure to platinum or etoposide-based chemotherapy induces occurrence of these mutations, which later populate the HSC compartment. *PPM1D* mutations are not known to expand in presence of other non-chemotherapy induced stresses, for example hematopoietic stem cell transplantation [38]. This observation, along with the relative absence of *PPM1D* mutations in *de novo* AML suggests that *PPM1D* mutations may only have leukemogenic potential after exposures to specific chemotherapeutics. Even among patients with t-MN, *PPM1D* mutations are generally present in relatively small VAF, thus suggesting that they comprise only a small part of the leukemic clone.

Although *TP53* and *PPM1D* mutations have been the major focus in mechanistic studies of t-MN, it is important to note that other CH mutations can also lead to t-MN and CH mutations in other DNA damage response genes have also been seen in 28% of patients exposed to chemotherapy [38]. For example, expansion of mutated *DNMT3A* clones, especially for the R882 codon, has been seen in

setting of transplantation induced stress and may have selection advantage in anthracycline-induced cytotoxic damage [1,55]. It is also important that not all expansion of CH clones in the setting of chemotherapy or transplantation-related stresses lead to the occurrence of t-MN. Furthermore, even when CH mutations are detected prior to t-MN, CH clones may not form the bulk of the neoplastic clone. Thus, additional cooperating events related to immunity, inflammation [56], the tumor microenvironment, concurrent mutations, germline risk (e.g. intronic deletion of *TERT*) [57], the microbiome [56], and a host of other factors, may play important roles in triggering the pathway to t-MN.

6. CH and hematopoietic stem cell transplantation

In the setting of stem cell transplantation, patients with CH are subject to a unique combination of cytotoxic stress and the added stressors of rapid HSC proliferation and bone marrow reconstitution. As discussed earlier, the presence of CH mutations can be detected in patients prior to exposure to chemotherapy and various stressors determine the ultimate trajectory and leukemic potential of these clones. While chemotherapy alone can be enough to cause selection of CH clones, auto and allogeneic transplantation provide an additional selection pressure, as the CH clones can expand rapidly, without any competition from the native, normal bone marrow cells. There is also evidence that, in allogeneic transplant recipients, telomere shortening is seen rapidly after HSC reconstitution, which itself can increase the risk of secondary cancers [58]. Furthermore, CH clones that reconstitute the marrow may have differential effect on tumor immunity; graft versus host disease (GVHD) and graft versus leukemia (GVL) as immune perturbations/inflammation are known to be associated with the presence of CH [1,59]. All of these factors make CH in the setting of transplant a potentially significant relevant risk factor for the development multiple adverse outcomes.

The presence of donor CH has been associated with slower count recovery in allogeneic transplant recipients [53]. Donor cell leukemia is a complication of transplant that is believed to result from rapid expansion of donor CH in the setting of hematopoietic recovery [60,61]. In this scenario, rapid expansion of CH in the recipient leads to AML, while the donors typically remain leukemia-free, even after many years of follow up. Although the exact incidence of donor leukemia is difficult to measure, it is probably underreported and may comprise up to 5% of post-transplant leukemic relapses [62].

Frick et al. assessed the effects of donor CH on 500 matched related donor hematopoietic stem cell transplant recipients [63]. The presence of donor CH was associated with increased incidence of chronic GVHD and reduced rates of relapse in patients whose disease was not in complete remission (CR) at the time of transplant, while no effect was seen on either cumulative incidence of relapse or transplant-related mortality in patients who were transplanted in complete remission. Two cases of donor cell leukemia were seen in this cohort, one of which acquired a *TP53* mutation over time. Disproportionately higher engraftment of CH clones relative to normal stem cells was seen in 10/11 recipients and, with the exception of one recipient, rapid engraftment and high VAFs seen after transplantation were not associated with an increased risk of leukemic relapse. Another study by Grim et al. (n = 113) showed no effect of donor CH on leukemia relapse while showing longer survival in recipients who had donor derived CH in *TET2* and *ASXL1* [64]. Furthermore, there was no difference in survival seen between having no CH, persistent donor CH or newly detected CH. It is important to note that both these studies did not have donor CH in *TP53* and there was only one donor CH in *PPM1D*. Data on *TP53* and *PPM1D* donor CH are lacking thus lacking with regards to ultimate risk of donor cell leukemia.

In contrast to the data reported for allogeneic transplant recipients, a higher risk of t-MN was observed in patients with CH after autologous stem cell transplantation (Table 1). In a study of 401 patients undergoing autologous transplantation for non-Hodgkin's lymphoma (NHL), CH was detected in 29.9% of patients (median age 61 years) prior to transplant [65]. *TP53* and *PPM1D* mutations were the most commonly detected mutations and at higher frequencies than expected based on population studies. The 10-year cumulative incidence of t-MN in the cohort was 7.6%, with 7.4% and 14.1% incidence at 5 and 10-year follow-up, respectively, in patients with baseline CH, compared to 1.7% and 4.3% at 5 and 10 years in patients without baseline CH ($p = 0.002$). Among patients with CH, the incidence of t-MN in patients with more than 1 mutation prior to ASCT was 25.3% at 10 years, compared to 9.9% for patients with only one CH mutation ($p < 0.001$). This is consistent with our finding in a population-based cohort in which the presence of multiple CH mutations was associated with a higher risk of AML compared to single mutations [13]. In a multivariable analysis, the risk of t-MN risk in autologous transplant patients was found to be significantly elevated in those with exposure to nucleoside analogues (cytarabine, fludarabine), $> 10\ g/m^2$ lifetime dose of cyclophosphamide, and the presence of CH. Interestingly, in patients with a t-MN sample available for testing, 5/9 had CH mutations present prior to autologous transplant that were detectable in the t-MN sample. Some patients had increased CH clone size upon evolution to t-MN, while for others, clonal mutations that were similar to the original CH clones were detected only in small VAFs at the time of t-MN diagnosis and did not comprise the bulk of the myeloid neoplasm. The risk of t-MN seems to be higher in patients with lymphoma who undergo autologous transplant compared to those who do not. In the study by Takahashi et al., the cumulative incidence of t-MN was 19% in patients who underwent autologous transplant, versus 2% in those who did not ($P = 0.003$) [33].

The different impact of baseline CH observed in allogeneic versus autologous stem cell transplant recipients suggest that the chemotherapy induced damage seen in the autologous transplant setting is instrumental in increasing risk of t-MN, along with the rapid expansion of CH clones that takes place as part of hematopoietic recovery. The impact of donor CH on outcomes in allogeneic HSCT needs to be further delineated with longer follow up and in setting of other donor types, including matched unrelated donors (MUD). For patients undergoing evaluation for autologous transplantation, the presence of CH is increasingly playing a role in guiding physicians to consider alternative treatment options. For example, if the risk of t-MN is assessed to be high (e.g. by the presence of *TP53, PPM1*D, more than 2 CH mutations, or high VAF of CH clones), allogeneic transplant instead of autologous transplant can be considered on a case by case basis.

7. Detection of CH in patients with malignancies: a clinical reality

CH mutations are increasingly and often inadvertently being identified in clinical practice as part of ongoing evaluations of other malignant and non-malignant diseases [66]. As CH mutations are not uncommon in patients with solid tumors (26.5%), genomic profiling of tumor tissue is likely to be contaminated with blood and, thus, CH mutations. In fact, data suggest that some mutations in tumor tissue actually arise from tumor infiltrating lymphocytes [67]. An analysis of matched tumor and blood sequencing by Ptashkin et al. revealed that approximately 5.2% of patients undergoing tumor sequencing would be erroneously reported as having a tumor mutation that is actually attributable to the presence of CH [68]. A similar study using commercially available solid tumor genomic testing suggested that 8% of tumor mutations detected in the study were actually due to confirmed CH, based on available blood samples. *DNMT3A* (64%) and *TP53* (4%) were among commonly present mutations that were erroneously reported as tumor-derived [69]. Another avenue of inadvertent detection of CH is the expanding field of cell free DNA testing (cfDNA) [70,71]. Hu et al. have estimated that 3% of patients had TP53 mutations detected in liquid biopsies of lung cancer that were only present in peripheral blood and not in tumor tissue [71]. CH mutations have also been known to contaminate germline testing for inherited cancer syndromes [72].

These misclassifications can have important clinical implications for patient care. The presence of CH mutations in patients undergoing treatment for solid malignancies has been associated with worse outcomes from progression of the primary malignancy and it is important to correctly classify the origin of the mutation. Moreover, erroneous decisions can be made if CH mutations are incorrectly identified as being tumor derived. For example, the presence of a *KRAS* mutation in tumor tissue would constitute a legitimate reason for not treating a colon cancer patient with cetuximab, but the presence of *KRAS* as part of CH contaminating tumor tissue should not preclude the use of this agent. Also, approximately 50% of erroneously reported CH mutations are considered oncogenic and targetable and may lead to incorrect treatment choices [69]. As more and more tumor tissue sequencing labs are classifying mutations as pathogenic or not and with a growing focus on precision medicine, decisions based on unmatched tumor and blood sequencing can lead to incorrect medical decisions. Correct identification of CH mutations in this context is also important for selecting the patients that need to be monitored for onset of t-MN.

8. Screening for t-MN: opening Pandora's box?

t-MN is associated with very poor survival and are one of the most devastating consequences of cancer survivorship. While prevention of t-MN is clearly an urgent medical need, there are currently many more questions than answers regarding the role of CH in the pathogenesis of t-MN and indiscriminate screening of chemotherapy-exposed patients would probably result in misguided interventions and untold anxiety. Still, we and others have advocated for prospective, large-scale monitoring studies of CH mutations in at-risk patient populations, with the objective of characterizing mutation-specific risks and identifying potential disease interception and, eventually, prevention strategies. The potential benefits of prospective monitoring studies in CH are not limited to t-MN. The presence of CH in patients undergoing chemotherapy has been associated with increased all-cause mortality, as well as increased risk of progression of the primary tumor [12,65]. Also, CH has been associated with increased cardiovascular mortality in general populations, thus influencing survivorship after cancer.

There are many other areas in which the presence of CH mutations at baseline prior to cancer therapy may influence clinical practice and more data in all of these situations are needed. Examples include:

- The presence of CH mutations, particularly *TP53* and *PPM1D* or other high risk driver CH mutations at baseline may influence chemotherapy selection and duration in individual patients.
- For selected patients with solid or non-myeloid hematological malignancies, the presence of high-risk CH mutations may prompt the use of more targeted treatments over chemotherapy if such agents are available in practice.
- For patients undergoing allogeneic transplant, the presence of CH has been associated with delayed count recovery and occurrence of chronic GVHD. Available data does not support the notion that donor CH is associated with worse leukemia relapse rates after allogeneic transplant.
- It is possible that the presence of certain CH mutations should preclude the application of autologous transplantation in certain cases and a careful discussion on alternative treatment options could be envisioned.
- Prevention-oriented clinical trials may become available for t-MN. For example, *PPM1D* inhibition via a small molecule inhibitor has been shown to induce apoptosis and prevent the penetrance of *PPM1D* mutant clones *in vitro* and *in vivo* when exposed to cytotoxic chemotherapy [50]. Such a strategy when combined with chemotherapy for select patients with CH may be attractive as a clinical trial.

9. Who should be screened in practice?

It is reasonable for patients to be routinely referred to hematologists with expertise in CH for evaluation of many clinical scenarios, including those listed above. Patients should also be referred for abnormal blood counts or CBC parameters, such as monocytosis, elevated RDW or incomplete blood counts after chemotherapy. Once CH is discovered either by proactive testing in presence of cytopenias or by inadvertent discovery via matched blood and tumor sequencing (cf DNA, genomic tumor sequencing, germline testing contamination), monitoring of these patients is recommended, preferably in the setting of a prospective clinical trial, if available. The frequency, modality, and nature of monitoring in this setting are controversial and patient-specific but, in general,

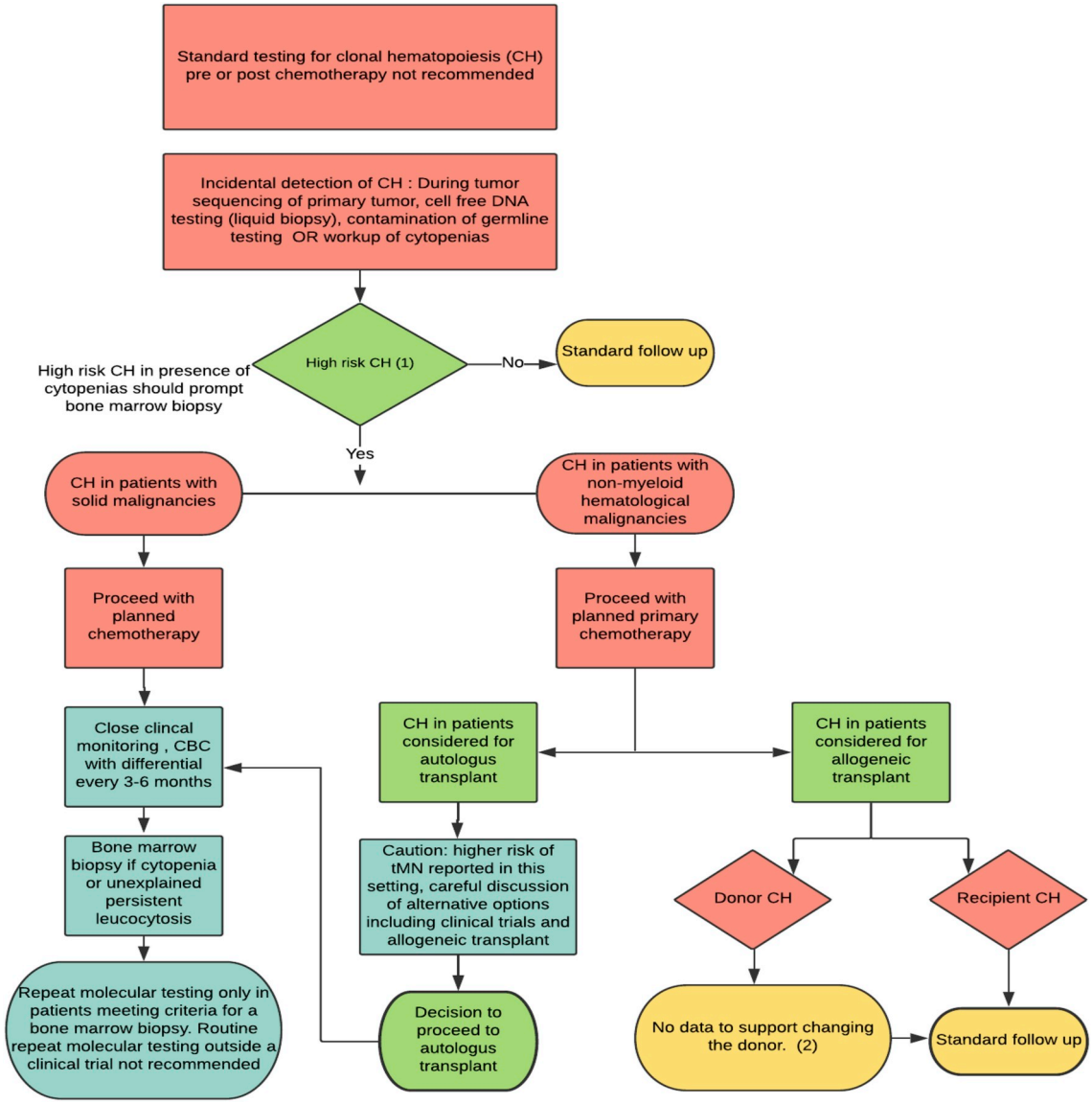

Fig. 2. Proposed follow up for patients with CH discovered incidentally or after workup of mild blood count abnormalities. (1) CH mutations can be defined as high risk if they satisfy any of the criteria: CH *with* TP53, PPM1D, DNMT3A R882H, presence of more than 1 mutations, VAF > 10% in driver mutations. This definition is subject to change as more data on mutation specific risk emerges in this setting. The optimal frequency of follow up is not evidence based at this point. (2) In the setting of allogeneic transplant, there are no data to support routine testing or change in donor selection based on presence of CH in the donor. No data on TP53 CH in the allogeneic setting available. One trial of AML patients treated with matched related allogeneic transplant showed an association of CH with increased incidence of chronic GVHD [63].

the CH mutation characteristics that are associated with the highest risk of t-MN should be taken into consideration, including:

- Mutations associated with high risk of t-MN or known to expand after chemotherapy stress (*TP53, PPM1D, DNMT3A* R882H)
- CH driver mutations with VAF > 10%
- Presence of more than 1 CH mutation

In these scenarios, relatively frequent monitoring of blood counts, every 3–6 months for up to 10 years is not unreasonable, as the incidence of t-MN in the setting of CH is known to be elevated up to 10 years based on available data. Abnormal blood counts, if confirmed, should prompt a bone marrow aspiration and biopsy for diagnosis (Fig. 2). Outside the scope of clinical trial monitoring and in absence of known ways to prevent or alter the course of t-MN, repeat mutation testing in patients with known CH is not recommended on a routine basis.

10. Challenges in prospective monitoring

There are many challenges in appropriate monitoring and prevention of t-MN in patients with CH. First, the exact spectrum of mutations to be monitored is controversial with several studies using a different set of genes based on local testing patterns. Although *TP53* and *PPM1D* mutations carry the highest risk of t-MN, not all t-MN arise from these clones and recognition of all of these clones that have leukemogenic potential is important. Standardization of the specific genes, cutoffs and methodology is needed. Second, the triggers to t-MN may not always be CH mutation specific and other cellular and external stresses, including inflammation and telomere attrition, may be important triggers that need to be identified to properly assess risk of t-MN. Third, a monitoring strategy only becomes relevant if intervention and/or prevention are ultimately possible. While the potential availability of targeted treatments is increasing, testing the utility and efficacy of prevention strategies is fraught with ethical and logistical challenges. The risks of over-testing and over-treating are substantial, and strategies for long-term monitoring of thousands of patients are needed. That said, there are clearly patients at higher risk for the development of t-MN in the short-term, and these are the patients who should be identified and targeted for intensive monitoring and evaluation in the context of a clinical study. Several such efforts are underway worldwide and participation should be strongly encouraged.

11. Summary

The presence of Clonal Hematopoiesis (CH) is associated with increased risk of therapy related myeloid neoplasms (t-MN), as well as increased risk of cancer-related and all-cause mortality. Patients with CH who are undergoing autologous transplant as well as patients with *PPM1D* and *TP53* CH mutations have a higher risk of t-MN. Patients with exposure to chemotherapy/radiation should be monitored clinically if high risk CH mutations are identified. Strategies to prevent t-MN are currently lacking and prospective trials are needed. Investigations related to cell intrinsic and extrinsic factors that govern the conversion of CH to t-MN will be instrumental in targeting the right patients for intensive follow up and prevention strategies.

Conflicts statement

Pinkal Desai and Gail Roboz: No conflicts to report with regard to the content of this article.

Practice points

- Clonal Hematopoiesis (CH) is being increasingly incidentally detected as part of workup of solid as well as hematologic malignancies, though active screening for CH is not recommended outside a clinical trial.
- The presence of CH before or after chemotherapy is associated with increased risk of t-MN but this risk is not absolute.
- CH patients should be monitored clinically with blood counts, no active intervention is recommended at this point.

Research agenda

- The mutation specific risk as well as clonal dynamics, including cell extrinsic factors that modify the risk of CH and t-MN needs to be determined.
- Prospective monitoring of CH mutations as part of clinical trial is an active area of investigation to determine the events that sets the path to the inevitable diagnosis of t-MN.
- Once patients that are destined to develop t-MN are determined, early intervention strategies need to be investigated to mitigate the risk of t-MN.

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