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Does early diagnosis and treatment of myelodysplastic syndromes make a difference?

David P. Steensma*

Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, Boston, MA, 02215, USA

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ABSTRACT

Patients diagnosed with myelodysplastic syndromes (MDS) often ask their physicians whether earlier detection of disease or more prompt initiation of treatment might have resulted in a better outcome. The concept of starting therapy at an early point in the disease process when the clonal burden of abnormal hematopoietic stem cells may be lower and somatic mutational complexity less, and therefore treatment more likely to be effective, is attractive. However, at present there is no evidence that therapy with any of the available drugs for MDS (ie, erythropoiesis stimulating agents, lenalidomide, azacitidine or decitabine) early after diagnosis is associated with better outcomes than later initiation of drug therapy. For those patients who are eligible for allogeneic hematopoietic cell transplant and have a suitable donor, early transplant of lower-risk MDS is associated with worse outcomes compared to nontransplant approach, whereas early transplant therapy of higher-risk disease improves outcomes compared to delaying transplant. Here I review available data about MDS diagnostic patterns and early versus later diagnosis and therapy initiation.

Introduction

Patients who are diagnosed with myelodysplastic syndromes (MDS) frequently have had minor blood count abnormalities for a prolonged period before a formal diagnosis of MDS was made. In one series of patients with MDS from England, for example, subtle changes in the blood counts such as red cell macrocytosis without anemia, increased red cell distribution width, or relative monocytosis were present for a median of ≥3 years prior to an MDS diagnosis [1]. Mild blood count abnormalities are especially common in elderly patients—more than 25% of Americans aged 85 years or older are anemic, usually due to nutritional deficiency, chronic endocrine renal insufficiency with inadequate erythropoietin production, or chronic inflammation suppressing erythropoiesis [2]—and perhaps due to their ubiquity and lack of obvious short-term clinical consequence, mild cytopenias are often incompletely evaluated in geriatric patients [3]. When geriatric patients with unexplained cytopenias are systematically evaluated including with marrow biopsy, a substantial proportion are diagnosed with MDS: 15% in one Israeli hospital series [4].

Because of the frequency with which there has been a long delay in evaluating blood count changes, patients ultimately diagnosed with MDS commonly ask their hematologist if, in retrospect, an earlier thorough evaluation and more prompt diagnosis might have made a difference in clinical outcome. Such questions must be understood within the context of a wider societal emphasis on early detection of cancer, including frequent public service announcements and media stories about the importance of routine mammography, endoscopic colorectal cancer screening, prostate-specific antigen (PSA) monitoring, and Papanicolaou cervical smears, all emphasizing the importance of “catching cancer early” before a small locus of disease metastasizes and treatment becomes more

* Dana-Farber Cancer Institute, D2037, 450 Brookline Ave, Boston, MA, 02215, USA.
E-mail address: David_steensma@dfci.harvard.edu.

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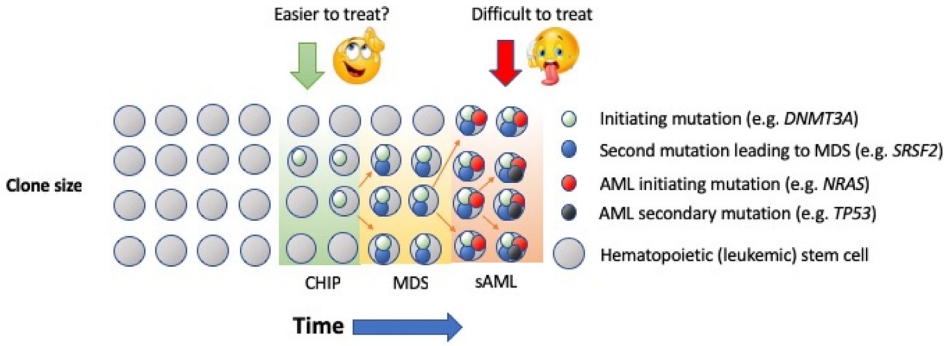

Fig. 1. Clonal hematopoiesis of indeterminate potential.
Clonal hematopoiesis of indeterminate potential (CHIP) may evolve to myelodysplastic syndromes (MDS) or secondary acute myeloid leukemia (sAML). While there is no established treatment for CHIP, the lower mutational burden and clone size may make this stage of disease easier to treat than the more complex/higher disease burden later stages. Colored circles represent leukemia driver mutations; grey circles represent hematopoietic stem cells.

difficult.

In contrast to solid tumors, there is currently no established screening protocol for early detection of any hematological malignancy in the general population. Instead, most patients with MDS present when symptoms such as fatigue, bruising and bleeding, or an infection develop, or when a blood count performed for another reason shows an abnormality and evaluation follows published guidelines [5]. This paper explores whether there is any evidence that early diagnosis or treatment initiation results in better outcomes for patients with MDS.

Clonal hematopoiesis and the diagnostic threshold of MDS

It is now understood that myeloid neoplasms usually arise from a state of clonal hematopoiesis that is common in elderly persons [6]. The subset of aging-related clonal hematopoiesis in which a mutation in a leukemia-associated driver gene (most commonly *DNMT3A, TET2, ASXL1, JAK2* or *TP53*) is present at a variant allele frequency (VAF) of at least 2%, but where there is no evidence of a myeloid neoplasm by conventional hematopathology, is termed "clonal hematopoiesis of indeterminate potential" (CHIP) and is present in more than 25% of people over 75 years [7]. The risk of CHIP progressing to MDS or acute myeloid leukemia (AML) is 0.5%–1% per year [8,9].

While most patients with CHIP have a single somatic mutation at a VAF of < 10%, by the time of diagnosis of AML, patients have a median of 4–6 mutations in leukemia driver genes [10] (albeit still a lower mutation burden than solid tumors [11]) and frequently have complex clinical architecture with multiple subclones [12,13]. It therefore makes intuitive sense that treatment of an emerging dominant clonal process at the CHIP stage might not only be easier than treatment of overt leukemia, but could prevent MDS or AML from ever developing (Fig. 1).

Several clinical trials trying to answer the question of whether there is benefit from treatment of CHIP are planned or ongoing. The recognition that a physiologically achievable concentration of vitamin C (ascorbic acid) can restore function of TET2 protein in preclinical models [14] prompted design of an interventional clinical trial (NCT #03682029) of vitamin C supplementation in both TET2-mutant myeloid malignancies—a trial for which patients with CHIP with cytopenias (ie, "clonal cytopenias of undetermined significance" or CCUS) are also eligible. Several other interventional trials for CHIP or CCUS patients have also been proposed recently, including isocitrate dehydrogenase inhibitors for patients with *IDH1* or *IDH2* mutations, or DNA hypomethylating agents following an abbreviated schedule pioneered at MD Anderson Cancer Center and the US MDS Clinical Research Consortium [15].

Since cardiovascular events are a more frequent complication of CHIP than hematologic neoplasia [16], and these events may be driven by clonally mediated inflammation that can be neutralized, trials of anti-cytokine molecules to try to reduce vascular complications have also been conducted. One such study was the CANTOS trial of the anti-interleukin-1β monoclonal antibody canakinumab in 10,000 patients with a prior myocardial infarction and persistent elevation of C-reactive protein, many of whom had CHIP. In the CANTOS study, canakinumab therapy resulted in a reduction of recurrent vascular events compared to placebo; the benefit was greater among those patients with CHIP [17]. The role of anti-cytokine therapy in MDS in contrast is unclear, and chronic anemia and volume shifts during repeated transfusions may obscure cardiovascular endpoints [18]. Trials of antibodies against tumor necrosis factor or interleukin 6 with a goal of improving hematopoiesis in MDS rather than preventing cardiovascular events have resulted in only modest benefits [19–21].

Early versus later diagnosis

For any disease, early diagnosis raises the possibility of lead-time bias (Fig. 2), which has confounded analysis of the benefits of tools such as mammography and PSA testing. In addition, if patients present earlier in a disease course and are diagnosed promptly, they have the opportunity to receive therapy earlier than those with a similar disease onset date and disease biology but for whom

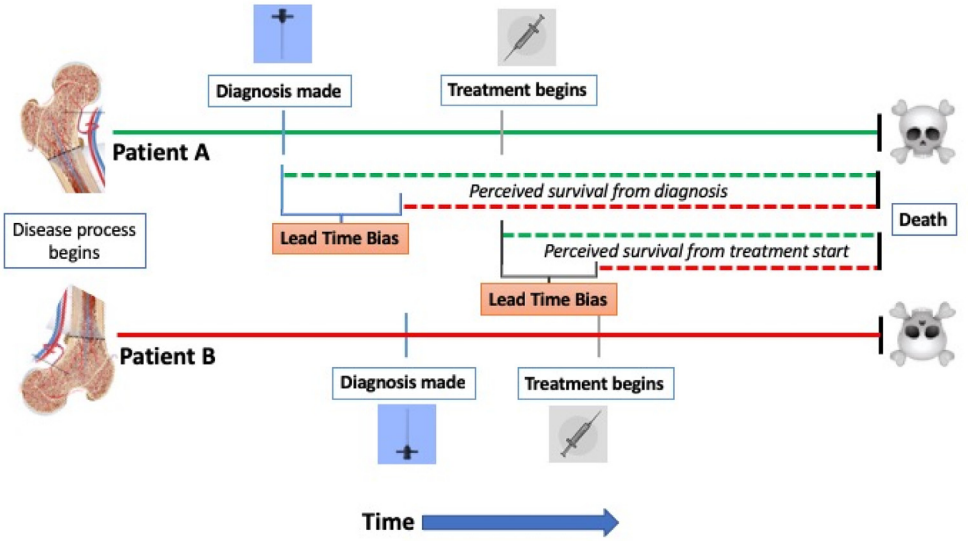

Fig. 2. Lead-time bias in diagnosis or treatment.
Lead-time bias in diagnosis or treatment can contribute to a false perception of improved outcomes.

there is a delay in diagnosis, which may make the therapy appear more effective early on even if it is not.

The clinical setting in which patients with hematologic neoplasms are diagnosed may be a surrogate marker for delay in diagnosis. In the Public Health England "Routes to Diagnosis" database [22], among 6402 patients in the United Kingdom who had hematologic malignancies other than acute and chronic leukemias (a group that included many patients with MDS), those who were referred by a general practitioner to a hematologist in the outpatient setting for diagnostic evaluation had a 12-month survival of 84% compared to those who were diagnosed as a hospital inpatient (72%) or in an emergency department (45%.) Diagnosis of MDS as an inpatient or in an acute care setting, however, may be a marker of greater comorbid conditions or illness severity, and may also be more common for patients with poorer access to care.

The minimal diagnostic criteria for MDS continue to be debated [23]. Patients who have unexplained cytopenias and lack dysplasia yet have a clonally restricted mutation (ie, CCUS) have a natural history similar to lower-risk MDS [24] and may be considered to have MDS in future revisions of the World Health Organization (WHO) classification, in the same way that in the current classification certain karyotypic abnormalities such as del(5q) may in the right clinical context be considered diagnostic of MDS even without dysplastic cell morphology [25,26].

Treatment patterns: time from diagnosis to initiation of drug therapy

Just as for diagnosis, when considering whether early treatment might be better than later treatment for any disease, lead-time bias for diagnosis falsely suggesting improved survival from the time of an earlier diagnosis and other confounding clinical variables must be considered. For instance, patients in whom treatment after diagnosis is delayed are by definition older than those who are treated soon after diagnosis, so comorbid conditions and frailty may have increased—particularly in patients who are transfusion dependent who may have complications related to iron overload and other transfusion-associated factors [27,28].

The majority of patients in the US who are diagnosed with MDS never receive any drug treatment. In an analysis of 5162 patients that was performed using the GE Centricity™ electronic medical record [29], 2079 (40.2%) patients received at least one treatment other than transfusion for MDS during the course of their disease [30]. For 1508 of these patients (29.0% of all patients diagnosed with MDS, and 72.5% of those who received any therapy), erythropoiesis stimulating agents (ESAs) were administered as the first-line therapy, despite the fact that ESAs are not approved for MDS by the Food and Drug Administration. Only 258 patients received lenalidomide as their first therapy while 105 patients received it as a later therapy (363 overall or 7.0% of all patients), and 252 patients received a hypomethylating agent (HMA) as first-line therapy while 344 received an HMA as second- or third-line therapy (12% overall).

Factors associated with early treatment of MDS were evaluated in the context of the CONNECT™ MDS/AML registry, an industry-sponsored national prospective observational registry with more than 160 enrolling sites and an accrual goal of 1500 patients [31,32]. Among patients with International Prognostic Scoring System (IPSS) lower-risk MDS, factors associated with earlier initiation of treatment included transfusion dependency, intermediate 1 IPSS risk category instead of IPSS low risk, marrow blast percentage of at least 5%, and performance of fluorescence in situ hybridization testing or molecular genetic testing by the treating center (possibly a marker of the volume of patients seen or of care quality). Among patients with higher-risk MDS, use of private health care insurance and a blast proportion of at least 10% were the only factors associated with early treatment initiation in a multivariable analysis. It is not known if early initiation of therapy resulted in better outcomes.

Specific drugs

While several studies have assessed factors associated with earlier use of specific drug therapies, none have clearly shown that earlier treatment is better. In a systematic review of 1314 patients enrolled in 30 studies of ESA treatment published between 1990 and 2006 (925 patients received epoetin, 389 darbepoetin), for example, there was a wide range in the median time from diagnosis to ESA therapy across studies (8–50 months), but there was not a clear association of earlier treatment initiation with higher likelihood of erythroid response to ESA [33]. Similarly, among 23,855 MDS patients with Medicare claims between 2006 and 2008 (the Medicare Part D prescription benefit went into effect January 1, 2006), 753 patients (2.3%) received lenalidomide [34]. While the median time to lenalidomide initiation was shorter for del(5q) MDS then for other lower-risk MDS subtypes (8 weeks vs 20 weeks, $P < .01$), the study was unable to assess whether earlier treatment was independently associated with better outcomes. The FDA label for lenalidomide is for patients who are transfusion-requiring; a SEER-Medicare analysis of lenalidomide use in patients with MDS who were not yet transfusion dependent showed increased adverse events and no benefit from treatment prior to onset of transfusion need [35].

The DNA hypomethylating agents (HMA) azacitidine and decitabine have disease-remitting activity in patients with lower-risk MDS [36], but are not approved for this use in Europe, and if HMAs are used early in the course of disease they are no longer available for later treatment at the time of disease progression. It is not clear that the survival benefit of azacitidine compared to conventional care seen in the AZA-001 study [37] of higher-risk patients extends to lower-risk patients. Patients with lower-risk disease treated with HMAs have similar hematopoietic response rates to those of higher-risk disease, however. For instance, in a multicenter study of 113 patients with IPSS low or intermediate-1 risk disease treated with an abbreviated schedule of either decitabine (n = 70) or azacitidine (n = 39), the complete response rate assessed using 2006 International Working Group criteria [38] was 37%, and the overall response rate was 70% with decitabine and 49% with azacitidine [15].

Treatment patterns: optimal timing of allogeneic hematopoietic cell transplant

One clinical setting where early intervention is clearly not associated with better outcomes is among patients with IPSS lower-risk disease (low/intermediate-1) sent for allogeneic hematopoietic cell transplant. In multisite Markov model decision analyses comparing life expectancy after either myeloablative transplant for younger patients [39] or reduced intensity conditioning transplantation for patients between 60 and 70 years [40], allogeneic transplant reduced life expectancy compared with conventional care for patients with IPSS lower-risk disease, but transplant offered a life expectancy benefit compared with either supportive care or HMA therapy for those with higher-risk (IPSS intermediate-2/high) disease.

Therefore, delaying allogeneic transplant for patients with lower-risk MDS and proceeding to transplant as soon as possible for those with higher-risk disease, possibly with HMA as bridging therapy until a donor can be identified, is current standard clinical practice [41]. With patients who have lower-risk disease, in contrast, watchful waiting and supportive care is appropriate, with transplant reserved for disease progression. Unfortunately, disease progression for lower-risk patients is not always gradual and may be abrupt. Patients who progress to MDS with excess blasts or to secondary AML often require cytoreductive therapy before they become eligible for transplant, especially if reduced intensity conditioning approaches are being considered [42]. Transplant decision-making based on patient risk group may also be influenced by the advent of next generation sequencing, and molecular genetic findings were not considered in the Markov analysis summarized above. Mutations in certain MDS-associated genes such as *RUNX1, NRAS, TP53* or *EZH2* increase the risk compared to that predicted by the IPSS or Revised IPSS [43,44].

Conclusion

At present, there is no convincing evidence that early diagnosis or early treatment are associated with better outcomes in MDS. Patients with MDS in whom long-standing pre-diagnosis minor blood count abnormalities were incompletely evaluated can therefore be reassured. However, the lack of data supporting benefit from early intervention may be because of a paucity of effective therapies for MDS, and if less toxic and more effective therapies that can eliminate clonal hematopoietic process become available, treating patients at an early stage before mutational complexity increases may become standard.

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