Prognostic factors and treatment of secondary leukemia

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Take Home Messages

- Prognosis of sAML is poor due to adverse karyotype, unfavorable somatic mutations, and patient frailty.
- New drugs with improved efficacy are in development.
- Patients should be enrolled in clinical trials using targeted treatments, which take into account the biologic characteristics of the disease.

Introduction

Under the definition of secondary leukemias (sAML) are included both diseases evolving from an antecedent hematological disorder (AHD), as myelodysplastic syndromes (MDS) or Philadelphia-negative myeloproliferative diseases (MPN), and leukemias or MDS diagnosed after exposure to a cytotoxic or immunomodulating drug given for a primary neoplasm or autoimmune disease (therapy-related myeloid neoplasms, t-MN). The group of t-MN is present in the WHO classification, while sAML evolving from an AHD are included in the category “AML with myelodysplasia-related changes (AML-MRC)”.

Current state-of-the-art

sAML are characterized by unfavorable prognostic features, with high frequency of poor-risk karyotypes, including monosomy of chromosome 5 or 7, del(5q) or del(7q), isochromosome 17p, loss or gain of specific chromosomes, complex karyotypes, 11q23 or 21q22 abnormalities, t(9;11), t(19;11) or t(4;11). However, karyotype does not fully account for the dismal clinical outcome of sAML, as illustrated by the inferior survival of sAML when compared to karyotype-matched de novo AML or IPSS-revised-matched MDS. Recurrent somatic mutations play a significant role in prognosis, with a high incidence of TP53 and splicing factor mutations being described in these forms. In many cases, somatic mutations are detectable at the time of primary disease diagnosis, also as part of clonal hematopoiesis of undetermined significance (CHIP) and likely favor the unstable environment for later expansion of minor clones, which in turn sustain secondary leukemogenesis. It is not clear whether this evolution occurs as part of the natural history of t-MN, or whether it is induced by the selective pressure of cytotoxic treatment used to treat the primary disease.

Survival in sAML is poor, when compared to other AML subtypes. The previous disease history and its treatment are significant factors contributing to patient frailty, and to unfavorable outcome. This highlights the need for careful collection of patient medical history, including details on exposure to specific agents and their cumulative dose, evidence of any organ dysfunction, and the remission status of the previous cancer. A detailed family history is also necessary to rule out familiar predisposition syndromes, which have been described in sAML, and are particularly relevant for the appropriate selection of allogeneic stem cell donors.

Until recent years, patients with sAML have been conventionally excluded from clinical trials, being this considered a severe disease, affecting a vulnerable population of older adults. While this attitude emphasized the role of antecedent disease and its treatment as determinants of outcome, more recent studies have shifted the focus on age, comorbidities and sAML biology as major prognostic factors and suggested a minor prognostic role of previous medical history itself. One of the preliminary question when dealing with patients with a sAML is in fact whether she/he is fit for conventional treatment. If this is the case, the most recent guidelines indicate that the choice should follow conventional ELN recommendations, and include allogeneic stem cell transplantation (HSCT), which remains the treatment option associated to best survival probabilities in most sAML (Figure 1). In these cases, induction prior to HSCT represents an issue. Conventional chemotherapy is associated to the highest complete remission (CR) rates, and the 7+3 regimen still represents the standard induction therapy in this setting. However, survival is significantly inferior in patients with complex karyotypes, despite similar CR rates, indicating the need for novel post-remission strategies. In this regard, novel minimal residual disease (MRD) techniques, including the combination of multiparameter flow cytometry and next generation sequencing (NGS) profiles, have shown a significant independent prognostic value for relapse and survival rates. The application of this approach may offer clinically helpful information also in the sAML setting.

In these patients, and in those who are not transplant-candidates, hypomethylating treatment (HMT), with azacitidine or decitabine, has shown to induce similar response rates comparing secondary and de novo leukemias. This may be due to the alternative mechanisms of action of HMT, which seems to overcome the negative prognostic value of karyotype, with similar response rates observed in patients with normal, as well as poor-risk karyotypes.
Treatment options

New treatment options have recently shown promising results in sAML and have received approval by FDA. Among these, CPX-351 is a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a 5:1 drug ratio (1 mg CPX-351 corresponds to 1 mg cytarabine and 0.44 mg daunorubicin). In a recent study, 209 elderly patients with sAML were randomized 1:1 to receive CPX-351 induction (100 units/m² on days 1, 3, and 5) versus 7+3 induction or 5+2 reinduction/consolidation. CPX-351 was associated to improved remission rates and significantly longer survival as compared to standard chemotherapy. Based on these results CPX-351 has become the first drug that was granted FDA approval in the specific setting of sAML.

Targeted-drugs, such as the inhibitor of mutant IDH2 enasidenib, have shown efficacy in a high-proportion of patients carriers of these mutations, which account for about 10% of sAML. In particular, enasidenib has been shown to induce differentiation of AML cells and complete remission (CR) in a high proportion of relapsed/refractory patients. Using this agent, differentiation syndrome is a potential secondary effect, which needs to be recognized and correctly approached.

Further recently approved drugs with wide application, without the need for intensive molecular screening prior to treatment start, include Venetoclax, Gentuzumab Ozogamicin and the single chain SGN-33A in CD33+ AML. Venetoclax, a highly selective, oral small-molecule BCL-2 inhibitor, is currently the only innovative drug with proven enhanced activity when combined with low-dose cytarabine or HMT. The combination was shown to be well tolerated and significantly improved response rates and survival in elderly unfit patients with AML, when compared to the standard arm. The survival prolongation was indeed due to improvement of quality and duration of responses, and achieved a “plateau” at 12-14 months of follow-up. This is an unprecedented observation in sAML ineligible for HSCT.

Future perspectives

Despite the approval of several new drugs in AML in the last year, sAML still represents a therapeutic challenge. In this heterogeneous, frail patient group, innovative treatment strategies are needed, which combine efficacy to tolerability. This objective

Figure 1. Treatment algorithm for sAML. The figure depicts patient stratification and treatment options in sAML. The definition of frail is according to Ferrara et al. PD, primary disease; AHD, antecedent hematological disorder; HMT, hypomethylating treatment; HSCT, allogeneic stem cell transplantation; St-CHT, standard chemotherapy.
will be only achieved by encouraging patient enrolment into clinical trials, with mandatory stratification according to clinical and molecular characteristics. This approach may open the way to the identification of specific and efficient new treatment options in this difficult setting.

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