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Secondary Acute Myeloid Leukemia: Pathogenesis and Treatment

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Abstract: Secondary acute myeloid leukemia includes acute myeloid leukemia that arises either from a previous myeloid hematologic disease such as myelodysplastic syndrome, chronic myeloproliferative syndrome, or myelodysplastic/myeloproliferative overlap syndromes or from a previous chemotherapy or radiotherapy performed for another disease. Secondary acute myeloid leukemia is characterized by a worse prognosis than its de novo counterparts, with a 5-year overall survival of <30% despite an advanced insight into pathogenesis and new available treatments. The best therapeutic strategy is to achieve complete remission with a negative minimal residual disease followed by hematopoietic stem cell transplantation; however, advanced age of patients at diagnosis, multiple comorbidities, and lower rate of complete remission makes these approaches available only for a small fraction of secondary acute myeloid leukemia patients. In this chapter, we discuss the epidemiology, pathogenesis, and prognostic

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factors of secondary acute myeloid leukemia. Also, we discuss the main treatments currently available for eligible patients (fit patients) and non-eligible patients (unfit patients) for intensive chemotherapy and future treatment perspectives.

Keywords: acute myeloid leukemia; secondary acute myeloid leukemia; acute myeloid leukemia with myelodysplastic-related changes; therapy-related acute myeloid leukemia.

INTRODUCTION

Acute myeloid leukemia (AML) with myelodysplastic related changes (MRC) are diagnosed based on clinical, cytogenetic, and morphologic criteria, reviewed in the 2008 WHO classification as those with a previous history of myelodysplastic syndrome (MDS), or myeloproliferative neoplasia (MPN) with specific cytogenetic alterations, or myelodysplastic changes in more than 50% of two or more cell lineages (1). The updated 2016 WHO classification excludes AML with dysplastic changes with NPM1 and CEBPA biallelic mutations or del(9q) from the MRC subgroup (2, 3). Next generation sequencing helped the comprehension of the pathogenesis of these entities, identifying mutations of RUNX1, TP53, SETBP1, epigenetic regulators, and spliceosome genes as those characterizing MRC-AML (4). Methylation of transcription factors, bone marrow microenvironment alterations such as neo angiogenesis, pro-inflammatory changes, and fibrosis acquisition, characterize the evolution of MDS into AML (5, 6). The most accepted model of leukemic evolution of MDS is the "two-hit" model with sequential blockade of genes regulating cell differentiation, such as TET2 or RUNX1, followed by alteration of genes regulating cell proliferation and survival (FLT3, NPM1, IDH1) (7, 8). Increased expression of the altered anti-apoptotic protein bcl-2 results in further stimulation of expansion of the dysplastic clone, which acquires a survival advantage over normal hematopoietic cells (8).

Secondary AMLs include both MRC and therapy-related AML (t-AML). This latter entity is defined as AML arising after exposure to chemotherapy or radiotherapy for previous cancer or autoimmune diseases and was first recognized by the 2008 WHO classification (1). Latency between primary disease and t-AML depends on age at diagnosis of the primary malignancy, type of cytotoxic treatment, cumulative dose, and dose intensity and its development might be influenced by genetic predisposition. Current ELN 2022 guidelines for diagnosis and cure of the disease removed t-AML and AML evolving from previous MDS or MDS/MPN, considering them only as diagnostic qualifiers (9). AML with myelodysplasia-related gene mutations (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2) and those with myelodysplasia-related cytogenetic abnormalities took the place of t-AML and MRC-AML, as the new entities of secondary AML, underlying the prognostic significance of molecular and cytogenetic features. Secondary AMLs are indeed characterized by an extremely poor prognosis and still represent a challenge for cure.

PATHOGENESIS

Chen et al. have shown that MDS is a disease characterized by several subclones with mutations in TET2, U2AF1 and TP53 genes which might acquire additional mutations, such as NOTCH2 and KMT2C, or later mutations associated with leukemic transformation such as RUNX1, NRAS and NTRK3. These complex subclonal mutations occur in stem cells determining MDS expansion or evolution into AML via variable mechanisms. Sequential single cell analysis technique may help the comprehension of these complex transformation mechanisms better than new generation sequencing (10). Lindsely et al. (11) analyzed mutations in 194 patients with secondary AML or t-AML (therapy-related acute myeloid leukemia) and in 105 de novo AML patients, identifying four different groups of mutations:

(i) *Secondary type mutations specific to secondary AML*: SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR and STAG2 capable of sustaining ineffective hematopoiesis, already at the diagnosis of MDS, without leading to the development of leukemia, which persist even after treatment, at clonal remission.
(ii) *De novo mutations:* NPM1, present in 5.4% of secondary AML, MLL/11q23 rearrangements, and CBF.
(iii) *Mutations in the TP53 gene (15.1% of secondary AML):* Acquired early in small subclones, less frequently expressing other mutations, but often associated with complex karyotype (12), expressed in 21.4% of de novo forms, characterized by poor prognosis.
(iv) *Pan-AML:* Mutations such as those of myeloid transcription factors (RUNX1, CEBPA, GATA2) and signal transduction proteins (FLT3 or RAS pathway), present in 78% of secondary AML, expressed equally in secondary and de-novo AML, absent in MDS, are responsible for leukemic evolution and disappear at remission.

Finally, the authors suggested three distinct ontogenetic patterns of AML MRC: the first is characterized by the presence of secondary type mutations, causing ineffective hematopoiesis, associated with a greater number of driver mutations, driving the evolution into AML; the second having de novo or pan-AML mutations, driving the evolution into AML themselves; and the third having TP53 mutations, acquired early, and associated with a lower number of driver mutations in comparison with the first group.

Lindsley et al. observed that similar genetic data were found in de-novo and t-AML patients, suggesting that these mechanisms are also applicable in t-AML pathogenesis and that the analysis of mutations might help to recognize MRC-AML in elderly de-novo AML patients, when secondary and TP53 mutations were observed (11). Another scenario characterizes MRC-AML secondary to MPN. Twenty-five per cent of MPN evolves in MRC-AML (13). Epigenetic regulators and mRNA splicing factors mutations, and primary "triple negative" myelofibrosis are more likely to undergo leukemic transformation. Mutations in splicing factor genes are associated with progression to secondary myelofibrosis and essential thrombocythemia (ET); TP53 mutations predict the risk of leukemic

transformation, and IDH1/2 mutations increase from 1–4% of chronic phase to 22% in blast-phase MPN (14).

Therapy-related AML

The WHO 2016 defines t-AML as those forms of AML that arise following exposure to chemo and/or radiotherapy for a previous neoplastic or not neoplastic disease. Breast cancer, non-Hodgkin lymphomas, and Hodgkin lymphomas are the three primary malignancies most frequently associated with the development of t-AML (15). Data from the Surveillance Epidemiology and End Result (SEER) register show that the incidence of t-AML increased from 0.04/100,000 people in the period 2001–2007 to 0.2/100,000 people in the period 2008–2014 (16). t-AML accounts for about 8% of all AML diagnoses with median age of diagnosis depending on the primary tumor, ranging between 40–66 years, which is reported to be 57.8 years in a retrospective analysis of 6 prospective multicenter trials of the German-Austrian AML Study Group (AMLSG) (15). It is associated with a poor prognosis, with a lower overall survival compared to de novo AML (15, 17, 18). The pathogenesis of t-AML is complex and still not fully known. To date, the most accredited theories include: (i) direct damage to the hematopoietic stem cells and the bone-marrow microenvironment mediated by chemo and radiotherapy; and (ii) pre-existing clonal hematopoiesis (19, 20).

The two classes of drugs that are associated with the development of t-AML are alkylating agents and topoisomerase II inhibitors (TOPII inhibitors). They generate double-stranded DNA breaks (DSBs) leading to growth arrest and cell apoptosis. If DSBs are not repaired, they can generate chromosomal alterations and genomic instability characteristic of these drugs (20, 21) (21–23). Radiotherapy determines either direct damage to the DNA, which can cause single or DSB, or an indirect damage to DNA through the generation of reactive oxygen species that can interact with DNA or nuclear proteins leading to modifications of DNA bases and/or DSBs (24, 25). Alkylating agents and radiotherapy often result in chromosome 5 and chromosome 7 abnormalities, complex karyotype, and TP53 mutation. AML occurs with a latency of 5–7 years and is often preceded by MDS. TopII inhibitors cause chromosomal translocations that most often involve the KMT2A genes on chromosome 11q23, RUNX1 on 21q22 and PML/RARA. The development of leukemia has a shorter period ranging from 1 to 3 years and is almost never preceded by a MDS (20, 26–28).

Bone marrow microenvironment, consisting of pluripotent mesenchymal cells and their descendants, endothelium of bone marrow sinusoids, fibroblasts, reticular cells, adipocytes, and catecholaminergic fibers, among others, regulate almost all functions of hematopoietic stem cells (HSC); it is therefore not surprising that the altered functions of these cells, caused by therapy, can contribute to the pathogenesis of t-AML (29–31). Cytotoxic agents cause the release of numerous pro-inflammatory cytokines (TNF alpha, IL-6, TGF beta) and the generation of free radicals that damage both the mesenchymal cells and the autonomous nerve fibers of the niche. Their altered functions, in several mouse models, have been shown to be sufficient for the onset of AML (32, 33).

Another pathogenetic mechanism hypothesizes that the presence of a clonal hematopoiesis of uncertain significance (CHIP) which, under the selective

pressure of chemo and radiotherapy, gain a proliferative advantage over the normal counterpart (34). This is supported by a case-control study where up to 71% of patients with a primary neoplasia had a contemporary CHIP; in these patients, TP53 mutation was present in 16% of cases. The cumulative incidence of t-AML was 30% in patients with a concomitant CHIP vs only 7% in those who did not have CHIP (35, 36). Furthermore, patients with t-AML present mutations on TP53 gene more frequently than patients with de-novo AML (33% vs 5–10% respectively) and these mutations are found, albeit with very low frequencies, in the bone marrow cells of those same individuals even before chemotherapy (37–41).

The development of t-AML is also a multistep process in which numerous somatic mutations accumulate, resulting in a progressive proliferative advantage and the arrest of differentiation in the pre-leukemic clone. The most frequently mutated genes in t-AML grouped into several functional groups are: (i) epigenetic regulators (TET2, DNMT3A, IDH1/IDH2, EZH2, ASXL1); (ii) regulators of the RNA spliceosome machinery (SRSF2, SF3B1, U2AF1); (iii) regulators of transcription (TP53, RUNX1); (iv) regulators of signaling pathways (FLT3) (37–39).

The t-AMLs are associated with poor prognosis with an estimated overall survival of 7–10 months (40), complete response (CR) rates of about 28–30% (41), and a shorter duration of response than de novo forms even after consolidation (42). The poor prognosis of these neoplasms depends on both patient-related factors and AML-related factors. Patient-related factors include older age at diagnosis, reduced bone marrow reserve from previous therapy as well as damage to the microenvironment, altered function of other organs as a complication of previous therapy, the need for prolonged immunosuppressive therapy due to a previous solid organ transplant, and the presence of the previous neoplasm still active. AML-related factors include TP53 mutation, and complex or monosomic karyotype, which are much more frequent in t-AML than de novo AML (43). However, the diagnosis of t-AML per se, does not contraindicate eligibility for intensive chemotherapy as some disease subgroups, such as those associated with the t(8;21), inv(16)(p13q22)/t(16;16)(p13;q22) or the t(15;17), have high CR rates (above 70%) and a 2-year overall survival of about 50% with this therapeutic approach, albeit still lower than the de novo counterpart (44, 45).

DEFINITION OF FITNESS TO INTENSIVE AND NON-INTENSIVE CHEMOTHERAPY

Scoring systems capable of predicting early mortality after intensive chemotherapy have not shown sufficient accuracy and reproducibility to ensure objective selection of patients fit for intensive chemotherapy. Rather, a recent work (46) has validated the 'Ferrara' criteria, selected by a group of experts from the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES), and the Italian Group for Bone Marrow Transplantation (GITMO), as a model capable of distinguishing patients fit for intensive chemotherapy, fit for non-intensive chemotherapy, or unfit for non-intensive chemotherapy (47). A list of 24 conceptual criteria was selected using a analytic hierarchy process-based consensus process, and on the basis of the pairwise comparisons of these

criteria, the members of the panel proposed the definition of unfitness to intensive chemotherapy as the presence of at least one of the following nine criteria: (i) age older than 75 years; (ii) congestive heart failure or documented cardiomyopathy with an EF ≤50%; (iii) documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm; (iv) dialysis and age older than 60 years or uncontrolled renal carcinoma; (v) liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and an age older than 60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis; (vi) active infection resistant to anti-infective therapy; (vii) current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver; (viii) ECOG performance status ≥3 not related to leukemia; and (ix) any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy). Patients fit for intensive chemotherapy are therefore those lacking all these clinical conditions.

The unfitness to non-intensive chemotherapy was defined as the fulfillment of at least one of the following six criteria: (i) refractory congestive heart failure; (ii) documented pulmonary disease with DLCO ≤65% or FEV1 ≤65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm; (iii) liver cirrhosis Child B or C or acute viral hepatitis; (iv) active infection resistant to anti-infective therapy; (v) current mental illness requiring psychiatric hospitalization, institutionalization or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver; and (vi) uncontrolled neoplasia. Patients fit for non-intensive chemotherapy do not fulfill any of these clinical conditions.

Obviously, these criteria did not take into account mortality rates related to newer low-intensity therapies, such as Venetoclax, IDH, and FLT3 inhibitors, associated or not with low-intensity chemotherapy or hypomethylating agents, where their accuracy has yet to be validated and explored, but they remain, at present, the best available clinical instrument for defining fitness to non-intensive chemotherapy.

TREATMENT OF PATIENTS FIT FOR INTENSIVE CHEMOTHERAPY

The current standard therapy for patients fit for chemotherapy is CPX-351, a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio, approved by FDA in 2017. A 5-year follow up of a Phase III trial in secondary AML confirmed an overall survival benefit of CPX over the standard 7+3, with a 10% increase in survival due to reduced early mortality and higher transplantation rate compared with 7+3 (gain of survival due to reduced early mortality and higher transplant rate in comparison to 7+3 (48). The transplant landmark analysis showed a higher number of transplanted patients, slightly older, in the CPX arm than in the 7+3 arm, having a 3-year overall survival rate of 56% versus 23% respectively (49). Improved transplant outcomes were not due to a decrease in

relapse, but to an improvement in non-relapse mortality with CPX, due to better tolerance of this induction approach compared to 7+3. This pivotal Phase III trial did not have the MRD data, but three real life data, the Italian, the French, and the German experience, showed respectively 57%, 57%, and 64% MRD negativity in responders (50–52). There is lack of data on the effect of CPX combination in FLT3 and IDH mutations. FLT3-mutated MRC-AML, fit for intensive therapy, should receive 3+7 with midostaurin; IDH-mutated patients do not yet have defined regimen for target therapy, but when ivosidenib and enasidenib achieve registration, they will represent an attractive therapeutic option.

CPX-351 combinations

V-FAST phase Ib trial accrued patients based on molecular profile: those with FLT3 and IDH2 wild type received CPX-351 plus venetoclax, those with either FLT3-ITDs or TKDs received CPX plus midostaurin, and those with IDH2 positive received CPX plus enasidenib (53). Venetoclax was administered as a short schedule, days 1–14, instead of days 1–28 of VIALE-A, to reduce hematological toxicity (Arm A). Midostaurin was administered along with the RATIFY schedule from days 8 through 21 (Arm B). Enasidenib was administered on days 8 to 28 (Arm C). Arm A enrolled 20 patients obtaining 50% CR/CRi (CR with incomplete hematological recovery rate), with similar median time to absolute neutrophil count (ANC) and platelet recovery in comparison to CPX351 phase III trial (48), in a very poor prognosis setting represented by 86% of the patients with intermediate and high-risk profiling, and nearly 30% of the patients with TP53 mutations. Thirty-day and 60-day mortality were low. The other two arms need to enroll additional patients before giving reliable results, but preliminary safety data show acceptable hematological recovery and a 0% early mortality rate, with responses achieved in all treated patients. The study is active, but not recruiting. MRC-AML might express FLT3 mutations. In the phase III study, 13% of patients had a FLT3 mutation on the CPX-351 arm versus 20% on the 3+7 arm. Trials combining FLT3 inhibitors with CPX351, quizartinib, and gilteritinib are ongoing and other regimens like the CLIA scheme (cladribine, idarubicin, cytarabine with gilteritinib) are under evaluation (NCT02115295). Trials on combination treatment with azacytidine, venetoclax, gilteritinib, and quizartinib are also under evaluation (NCT03661307, NCT04140487).

CPX-351 in patients with MDS and prior hypomethylating agent exposure

Phase III data of CPX-351 did not show an advantage in comparison to 7+3 in patients with secondary AML and prior MDS, who received prior therapy with hypomethylating agents, such as azacitidine and decitabine. A retrospective analysis compared outcomes of 242 patients affected by AML secondary to MDS who were pre-treated with hypomethylating agents, after three induction strategies: CPX-351 versus 7+3 versus CLAG-M (cladribine, cytarabine, G-CSF, and mitoxantrone) (54). Patients receiving the CLAG-M regimen, achieved a 53% CR/CRi rate, higher than that observed with CPX-351 (41%) and 7+3 (32%), with similar median overall survival accounting for 7.27, 7.07 and 7.63 months respectively. The sample size and multicenter enrollment make this real-life experience

indicative of real-world outcomes, even with the limitation of being a retrospective study. Patients receiving less than four cycles of hypomethylating agents had a better response rate of 64%, and 6-months analysis showed that those receiving CPX-351, followed by allogeneic transplant, had a better overall survival in comparison to all other patients. Allogeneic transplant conferred a survival advantage in all treatment arms.

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HCST) represents the only curative option for the treatment of MRC and t-AML. A retrospective Italian study showed a median overall survival of 58.8 months in patients after HCST (55). Litzow et al. analyzed 545 t-AML undergoing HCST and showed an overall survival of 22% at 5 years. The rapid identification of a suitable donor and the choice of a bridge to transplant with better extra hematological tolerance are the foundations of a successful cure. In a phase III trial, 31% of patients transplanted after CPX-351 treatment were over 70 years vs 15% transplanted after 3+7. Elderly t-AML patients who achieved a response after CPX-351 had better post HCST overall survival and a higher rate of transplantability, compared with those responding after 3+7 (56).

A retrospective analysis of the European Group for Bone marrow Transplant (EBMT) analyzed 802 secondary AML patients, median age of 59.6 years, undergoing HSCT after a myeloablative conditioning (MAC) in 40% of cases and a reduced-intensity conditioning (RIC) in 60%. They showed a 2-year cumulative recurrence incidence (RI) of 37%, leukemia-free survival (LFS) of 40%, overall survival (OS) of 46%, non-relapse mortality (NRM) of 23%, and chronic graft-versus-host disease (cGVHD) of 39%, with similar results between conditioning regimens. Patients in the MAC group had better RI (hazard ratio [HR], 1.79; P <. 05), LFS (HR, 1.43; P = .02) and OS (HR, 1.53; P = .005) in comparison with those receiving a RIC regimen. There was no difference in the cumulative incidence of NRM (HR, 1.38; P = .15) (57).

Allogeneic HCST is the best long-term treatment strategy for high-risk patients compared with chemotherapy alone (58). Myeloablative regimens had a lower risk of recurrence and higher LFS and overall survival than RICs, with no statistically significant difference in NRM. The decrease in the incidence of recurrence is concordant with a recent phase III study by Scott et al. in which patients with AML/MDS who received myeloablative conditioning had a statistically significant higher recurrence-free survival rate and a nonsignificant trend toward improved overall survival (59). This study showed no difference in NRM between the two conditioning groups, suggesting improvement in supportive care and management of post-transplant complications (60).

TREATMENTS OF PATIENTS UNFIT FOR INTENSIVE CHEMOTHERAPY

The criteria of patients who are unfit for intensive chemotherapy is defined above under "*Definition of fitness to intensive and non-intensive chemotherapy*".

Venetoclax and hypomethylating agents

The high expression of bcl2 protein in AML blasts and the preliminary efficacy and safety of venetoclax in monotherapy (61) are the reasons for the VIALE-A phase III trial. It randomized 145 patients on azacitidine alone and 286 patients on azacitidine plus venetoclax. The CR/CRi was 67% with a hazard ratio of 0.56 for the combination group whereas it was 23% CR/CRi for azacitidine alone (62). Even though the data on the combination of hypomethylating agent and venetoclax are encouraging, they are modest in TP53-mutated patients, and the addition of venetoclax to the 10-day decitabine scheme did not result in any particular benefit with regards to overall survival and relapse-free survival compared to historical results with 10-day decitabine alone (63). VIALE-C showed that the combination of low dose cytarabine and venetoclax did not result in survival advantage, in comparison with low dose cytarabine alone in secondary AML (64). Outcomes of t-AML patients, representing 8–9% of all enrolled subjects, were not reported in these trials.

A retrospective observational study analyzed 217 patients treated with CPX-351 and 439 patients treated with venetoclax/azacitidine; the patients had a balanced distribution of European LeukemiaNet risk, high risk mutations (TP53, ASXL1, RUNX1), FLT3, IDH, and hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (65). Overall survival, tolerance, and early mortality were similar in both two groups, but infections and febrile neutropenia were more frequent in CPX-351 patients vs venetoclax/azacitidine, with a median overall survival of 13 months in the CPX-351 group and 11 months in the combination group. Multivariate analysis did not identify any predictive factors of response to therapy, but HSCT was associated with significantly improved survival. These outcomes were confirmed when analysis was restricted to patients who met the eligibility criteria of the phase III CPX-351 trial. The main pitfall of the study is the lack of MRD data.

The phase III AZA-AML-001 study comparing azacitidine vs conventional care regimens including 7+3 intensive chemotherapy, low doses of ara-c (LDAC), and supportive care showed a survival advantage in the azacitidine arm vs conventional care regimens arm with one-year survival of 46% vs 32%, respectively (66). The study enrolled 488 elderly patients with newly diagnosed AML, and of these, 262 had AML with myelodysplasia-related changes (AML-MRC). Even in the AML-MRC subgroup, the survival advantage in the azacitidine arm over the conventional care regimens arm was maintained (one-year survival 44.3% vs 27.2% respectively). Within the patient's group with AML-MRC, overall survival was higher in those with multilinear dysplasia on morphologic examination than in patients with cytogenetic alterations defining AML-MRC (67). The median overall survival in patients with morphologic dysplasia in the azacitidine arm was 16.3 months vs 5.3 months in patients with cytogenetic alterations diagnostic for AML-MRC (68).

Decitabine administered for five consecutive days was compared to treatment choice (TC) (LDAC or supportive care) in 485 older patients with newly diagnosed AML in a phase III randomized multicenter trial (69). In this trial, decitabine did not demonstrate a significant improvement in median overall survival compared to TC (7.7 months vs. 5 months) and this result was also true for 171 patients with secondary AML (69, 70). In a phase II study, in 19 patients with AML-MRC

aged ≥60 years, decitabine administered for 10 consecutive days (71) showed an overall response rate (CR + CRi) of 74% (95% CI: 49–91%). Although hypomethylating agents are commonly used in the treatment of AML-MRC patients, to date, no head-to-head comparison between azacitidine and decitabine has been performed. However, from the combined analysis of the five published phase III randomized control trials on hypomethylating agents seem to suggest an overall survival advantage of azacitidine over decitabine (HR for azacitidine 0.67, 95% CI: 0.56–0.79, P < 0.00001; HR for decitabine 0.86, 95% CI: 0.73–1.02, P = 0.08) (72).

JAK inhibitors

Ruxolitinib as monotherapy resulted in modest responses in phase II studies in transformed JAK2 mutated MPNs (73, 74). Decitabine alone extends survival to 9–10 months in advanced MPN with a better safety profile than intensive chemotherapy regimens (75, 76). Azacitidine and ruxolitinib combination was explored in chronic phase primary myelofibrosis (PMF) in a phase II study at the MD Anderson Cancer Center resulting in high rates of reduction of splenomegaly and fibrosis (77). A combination of ruxolitinib 50 mg, twice a day, and decitabine was explored in a phase I/II study in blastic phase (BP) patients with an overall response rate of 61% and a median overall survival of 8.4 months (78). Mascarenhas et al. combined ruxolitinib at a reduced dosage of 25 mg twice daily for the induction cycle and 10 mg twice daily for subsequent cycles in combination with decitabine 20 mg/sm for 5 days, in a phase II study enrolling 25 PMF patients in AP/BP (advanced phase/blastic phase), achieving an overall response rate of 44% and a median overall survival of 9.5 months. The survival data equaled that of intensive chemotherapy followed by HCST, (23) but it appears that the addition of ruxolitinib, results in better responses in terms of rate and duration, compared to decitabine alone, due to the reduction in splenomegaly (median reduction, –54.8%) with a positive impact on quality of life, unaffected by TP53 expression (79).

Future Perspectives

The peculiar biological characteristics of MRC and t-AML, induce chemoresistance and poor tolerance to the classic 7+3. CPX-351 and hypomethylating agents/venetoclax represent the current standard of care, but the mutational landscape deserves new possible target therapy in the repertoire of future clinical trials. IDH inhibitors (IDHi), antibody targeting CD47, and anti TP53 drug eprenetapopt (APR246) might represent possible target agents deserving further evaluation in combination with hypomethylating agents in MRC-AML. New MDM2 (murine double minute 2) inhibitors, and BET (bromodomain and extraterminal) inhibitors also show activity in advanced, accelerated-phase PMF, and could be extended to AML evolving from an underlying MPN. Several phase I and II clinical trials have shown promising results in this unfavorable setting and support the rational for the design of future trial of combinations of new drugs. For instance, anti PD-1 nivolumab in association with azacitidine provided a CR/CRi rate of 39% in 31 relapsed refractory secondary AML (80). The small molecule TP53 inhibitor eprenetapopt was able to restore mutated TP53 and showed a 56%

CR rate in a phase II trial in combination with azacytidine (81). The anti-CD47 antibody magrolimab (Hu5F9-G4) demonstrated a 67% CR/CRi rate in combination with azacytidine in TP53-mutated AML with an overall survival of 12.9 months (82). The bispecific DART molecule targeting CD3-CD123 achieved a 39% CR in a phase I/II study in 38 relapse/refractory AML (83). Menin inhibitor SNDX-5613 showed a 24% CR/Cri and a 50% overall response rate in a phase I study, with NPM1, MLL or KMT2A AML mutations, expressed by 40% of AML, predicting response (84). CPX-351, hypomethylating agents+venetoclax, 7+3+midostaurin are the current golden standard for the treatment of unfavorable disease respectively in fit, unfit, and FLT3 mutant MRC and t-AML. Poor cytogenetic and molecular risk, in addition to the older age of these patients, are the main limitations for cure, and allogeneic transplant remains the only curative option. Double or triple combinations of some of the above drugs with hypomethylating agents and/or venetoclax or CPX-351 might deserve further exploration in future phase III trials, tailoring therapies, based on molecular repertoire and patient fitness, aiming to increase both cure and quality of life.

CONCLUSION

Secondary AML are extremely heterogeneous diseases, characterized by poor prognosis. The study of the pathogenesis of this entity has led to the identification of a number of mutations specific to secondary AML (11). The latest revision of the ELN guidelines for the diagnosis and treatment of AML not only lowered the cut off of blasts to 10%, by identifying the new entity of AML/MDS in the presence of these specific mutations, but also eliminated the entity of MRC AML, replacing it with the 'AML with myelodisplastic related gene mutations', having at least one of the pathognomonic mutations (ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2) and lacking a specific cytogenetic alteration, diagnostic of AML with myelodysplasia-related cytogenetic abnormalities. This means that the prognostic significance of AML molecular features overcomes that of a previous history of hematological disorder or exposition to chemotherapy and radiotherapy, underlying the correlation between such mutations and resistance and refractoriness to standard therapies. CPX-351 remains the gold standard in patients eligible for intensive chemotherapy, with the chance of a potential improvement after combination with venetoclax and FLT3 and IDH inhibitors, currently under investigation (53). A better understanding of the pathogenesis of the disease may guide preclinical research for future targets, worthy of tailored therapies, especially in patients pretreated with hypomethylating agents, where current real-world experience shows improved OS in transplanted patients after CPX-351 (54). Current supportive therapies, which can certainly be implemented, have already determined an improved outcome of HSCT after MAC conditioning, as shown in a recent EBMT survey, with an NRM rate of 23%, similar to that observed after RIC conditioning (57), which was still burdened by worse LFS, without a significant reduction in OS. Therefore, the 2-year recurrence incidence of 37% remains the main obstacle to overcome, to improve the cure of the disease. An area of future research will certainly be the modulation of minimal residual disease after transplantation, through maintenance therapy with FLT3 inhibitors

and the use of pre-emptive therapy with target and immunologic drugs, such as anti-CD47 or anti-CD123 monoclonal antibodies, in addition to currently available hypomethylating agents.

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