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Novel therapeutic options in Acute Myeloid Leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is a biologically complex and molecularly and clinically heterogeneous disease, and its incidence is increasing as the population ages. Cytogenetic anomalies and mutation testing remain important prognostic tools for tailoring treatment after induction therapy. Despite major advances in understanding the genetic landscape of AML and its impact on the pathophysiology and biology of the disease, as well as the rapid development of new drugs, standard treatment options have not experienced major changes during the past three decades. Especially for patients with intermediate or high-risk AML, which often show relapse. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the best chance for cure. Here we review the state of the art therapy of AML, with special focus on new developments in immunotherapies and cellular therapies including HSCT and particularly discuss the impact of new conditioning and haplo-identical donor regimens for HSCT, post-transplant strategies for preventing and treating relapse, and emerging novel therapeutic options.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous disorder characterized by clonal expansion of blasts (myeloid progenitors) in the bone marrow and peripheral blood. Formerly, AML had a very poor prognosis; due to improvement in therapeutic regimens and supportive care (e.g. anti-infective drugs, blood transfusion support), AML is now cured in approximately 35–40% of patients younger with age younger than 60 years [1]. For elderly patients (> 60 years), the prognosis has also improved, but overall remains adverse. Molecular screening plays a major role in prognostic categorization and subsequent definition of treatment strategies in AML. Cytogenetic abnormalities (e.g. deletions, translocations), as detectable in approximately 50% of adult patients with primary AML have long been associated with and recognized cause [2]. Of these, for example alterations of chromosomes 5, 7, 11q23 and a complex karyotype (described as > 3 chromosomal abnormalities) were shown to associate with poor response to therapy and shorter overall survival (OS) while the presence of other cytogenetic abnormalities like t(15;17)(q22;q12), t(8;21)(q22;q22) or inv(16)(p13.1;q22) indicate longer disease remission and patient survival [1,3]. In contrast, about 40–50% of all AML cases are cytogenetically normal AML (CN-AML) [3]. CN-AMLs are considered to have an intermediate risk for relapse. However, with respect to clinical outcome substantial heterogeneity is observed in this group, which indicates that further prognostic markers to be evaluated. More recently, the identification of mutations by gene sequencing has provided novel prognostic and potentially therapeutical tools for patients with AML.

2. Prognosis/risk stratification

Besides age and performance status, cytogenetic and molecular aberrations are the most important tools to predict outcome in AML [3]. In 2010, the European LeukemiaNet (ELN) classification scheme was created with the aim to standardize risk stratification in adult AML patients by including cytogenetic and known molecular abnormalities [4]. Patients are classified into one of four risk groups: favorable, intermediate 1, intermediate 2 and adverse (Table 1). Of note, acute promyelocytic leukemia (APL) is excluded from the ELN classification and also not discussed in this review, as APL requires highly specific prognostic, therapy and monitoring approaches that are largely different from those applied to other forms of AML.

3. AML therapies with curative intent

3.1. Induction Therapy

The backbone of anti-leukemic treatments with curative intent builts on intensive induction chemotherapy regimens. The composition of induction therapies has remained largely unchanged over more than 4 decades. For young adults (age < 60 years) and fit elderly patients

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Table 1
European LeukemiaNet (ELN) risk group classification (adapted from Ref. [4]).

Genetic group	Subsets
Favorable	t(8;21), inv(16) Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate I	Wild-type NPM1 (normal karyotypes) FLT3-ITD (normal karyotype)
Intermediate II	t(9;11); MLLT3-MLL Cytogenetic abnormality not classified as favorable or adverse
Adverse	inv(3) or t(3;3) t(6;9) t(v;11) −5 or del (5q); −7; abnl (17p); complex karyotype

Abbreviations: abnl, abnormalities; CEBPA, CCAAT/enhancer-binding protein alpha; del, deletion; FLT3-ITD, Fms-related tyrosine kinase 3-internal tandem duplications; MLLT3-MLL, mixed lineage leukemia; NPM1, nucleophosmin 1.

(especially if belonging to favorable prognostic groups according to ELN criteria; see Table 1) the intensive anthracycline and cytarabine regimen, "3+7", induction therapy is standard of care [5]. The aim of induction chemotherapy is to achieve complete morphologic remission (CR) in curative intent [6]. Using standard induction with "3+7", higher morphologic CR rates are observed in young, de novo, versus elderly (> 60 years) AML patients (65–73% versus only 38–62%) [7,8]. The poorer CR rates observed in elderly versus younger patients are due to more often observed patient co-morbidities that limit they dose-intensity of applied therapies, but may also result from inherent differences in disease biology, since secondary, therapy related and high risk AML – according to molecular criteria – are overrepresented in this group. Several trials have now shown that further enhancing the dose of anthracycline (from 45 to 90 mg/m^2) augments CR rates and OS in both younger and 60–65 years old fit adults, reinforcing the notion that dose-intense chemotherapy is required to achieve cure [9]. However, enhanced toxicity is also observed with dose intensification. Thus, the grading of fitness is important when deciding which treatment strategy is most appropriate [10]. Besides assessment of the AML risk group (see Table 1) the choice of intensive therapy for elderly AML patients requires careful evaluation of the patient's fitness, vulnerability and frailty and should be assessed using standardized geriatric assessment tools rather than based on calendaric age (reviewed in detail in [11]).

3.2. Consolidation therapy

The main aim of consolidation therapy is to prevent relapse by eradicating minimal residual disease (MRD) still present in the bone marrow after induction therapy [2]. For AML patients presenting with molecular abnormalities, the depth of response after induction therapy and during the course of the disease can be assessed at minimal residual disease level using real-time polymerase chain reaction or Next Generation Sequencing (NGS). Recent studies suggest that adding molecular criteria to the morphological assessment is superior with respect to prediction of imminent relapse, and therefore may be a useful guide for treatment decisions [12,13]. There are two main options for consolidation therapy: chemotherapy (including targeted agents) and hematopoietic stem cell transplantation (HSCT) [14]. These strategies are used alone or most commonly in combination. In younger adults (< 60 years of age) with favorable risk AML, post induction chemotherapy using intermediate-dose cytarabine 1.5 g/m^2 twice daily on days 1, 3 and 5 given in three to four cycles is an effective and established regimen to prolong remission and improve survival [5,15]. These patients are thus usually treated with chemotherapy alone and transplantation is reserved only at relapse [5,15]. In the HOVON/SAKK group, a third cycle of chemotherapy with mitoxantrone and etoposide is used as consolidation therapy [14]. In contrast, patients suffering of intermediate or high-risk AML commonly receive high-dose chemotherapy (as bridge to transplant) followed by HSCT; overall, therapy is tailored depending on the aggressiveness of the AML, but also the fitness of the patient and the availability of a stem cell donor.

3.2.1. Allogeneic hematopoietic stem cell transplantation

Particularly in fit patients that suffer of intermediate or high-risk AML and achieve CR after induction therapy, allogeneic HSCT remains the most effective long term treatment yielding cure in 50–60% of patients [14,16–18]. Nevertheless, several patients never become eligible for transplant because of co-morbidities, failure to reach CR or lack of a suitable donor [1,2,16]. While waiting for transplant, it is standard practice to give post induction chemotherapy to maintain CR and keep the leukemia burden low. Eligibility for transplant is decided upon based on pre-transplant performance status, co-morbidities and current remission. The most widely recognized and validated tool for assessing comorbidity includes the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) [19]. The higher the comorbidity index score, the worse the clinical outcome. Improvements in supportive care, increased donor options (haplo-identical donors and cord grafts) and reduced intensity preparation regimens for HSCT have increased the success of transplant in all age groups.

One of the most important treatment decisions in AML is to estimate the benefit/risk ratio of allogeneic HSCT for a given patient in first CR. Transplantation offers the best means of preventing AML recurrence, but remains associated with higher treatment-related morbidity and mortality (TRM), especially in elderly patients. In patients with favorable-risk AML, the relapse risk may be low enough and the salvage rate high enough to postpone HSCT to second remission. This strategy has been validated in several donor versus no-donor studies [18,20]. In these studies, favorable patients (i.e., those with CBF-AML) from the no-donor group did as well as those from the donor group, whereas all other patients appeared to benefit from undergoing allograft. One should keep in mind that patients in these studies mostly underwent sibling donor myeloablative conditioning (MAC) transplantation and as such, the benefit associated with HSCT was only demonstrated for patients < 40 years of age. Based on another donor versus no-donor analysis, patients with CN-AML and a favorable genotype defined as mutated CCAAT/enhancer-binding protein alpha *(CEBPA)* or nucleophosmin 1 (*NPM1)* without Fms-related tyrosine kinase 3-internal tandem duplications *(FLT3*-ITD) were recently categorized in the favorable subgroup [4]. Because the outcome after allogeneic HSCT from fully matched unrelated donors appears to be similar compared with allogeneic HSCT from matched related donors, all younger patients with intermediate- and unfavorable-risk AML are generally considered candidates for allogeneic HSCT from sibling or fully-matched unrelated donors in cases of first CR [16].

This HSCT benefit/risk assessment, based on the European LeukemiaNet (ELN) genetic classification only [4], needs however to be reconsidered in the near future. Alternative stem cell sources are more widely used and are safer, as illustrated by post-transplant administration of cyclophosphamide in haplo-identical HSCT [16,21].

In a recent survey of the EBMT (European Society for Blood and Marrow Transplantation) by Passweg et al., a record number of 40.829 HSCT in 36.469 patients (15.765 allogeneic (43%), 20.704 autologous (57%)) were reported by 656 centers in 47 countries. The trends in the report included a continued growth in transplant activity, more so in Eastern European countries than in the west; a continued increase in the use of haplo-identical family donors (by 25%) and slower growth for unrelated donor HSCT. The use of cord blood as a stem cell source has decreased again in 2014 [16].

A recent study by Versluis et al. showed that allo-cHSCT might be