ACUTE LEUKEMIA
AKUTNE LEUKEMIJE

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CURRENT STRATEGIES FOR THE TREATMENT OF ACUTE MYELOID LEUKEMIA

SAVREMENI VIDOVI LEČENJA AKUTNE MIJELOIDNE LEUKEMIJE

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Summary

Introduction. Acute myeloid leukemia is a rare malignancy with an average age of 70 years at diagnosis. Until recently, five-year survival of younger patients with this disease, despite being treated with allogenic hematopoietic stem cell transplantation, was < 30%, while in patients older than 60 years it was < 10%. **Treatment overview.** Due to the heterogeneity of acute myeloid leukemia no new drugs for treating this disease have been introduced for decades. The introduction of new drugs began from 2017: midostaurin, gilteritinib, CPX351, enasidenib, ivosidenib, venetoclax, glasdegib, while gemtuzumab ozogamicin has been reintroduced. Modern treatment strategies require an individual approach, based on prognostic parameters such as cytogenetical and molecular profile of acute myeloid leukemia at diagnosis and the assessment of minimal residual disease evaluated after two cycles of chemotherapy. Moreover, determining the eligibility of patients for ''intensive'' treatment, based on functional status, comorbidities and geriatric assessment of older patients, is necessary. Regarding the treatment of acute promyelocytic leukemia, the combination of arsenic trioxide and all-trans retinoic acid is universally accepted as the standard of care for non-high risk patients (WBC < $10x10^9$/L), while standard chemotherapy combined with all-trans retinoic acid is still used for high-risk patients (WBC >$10x10^9$/L). **Conclusion.** Novel therapeutic modalities, along with allo-HSCT have changed the outcome of AML patients. However, treating patients unfit for intensive chemotherapy, as well as patients with relapse/refractory disease, is still challenging.

Key words: Leukemia, Myeloid, Acute; Therapeutics; Prognosis; Risk Assessment; Treatment Outcome

Sažetak

Uvod. Akutna mijeloidna leukemija je redak malignitet čija je medijana uzrasta prilikom dijagnostikovanja 70 godina. Sve donedavno, petogodišnje preživljavanje mlađih pacijenata je, uprkos alogenoj transplantaciji matične ćelije hematopoeze bilo < 30% dok je kod pacijenata starijih od 60 godina bilo < 10%. **Savremeni terapijski pristup.** Decenijama nije bilo novih lekova za akutnu mijeloidnu leukemiju što je posledica izrazite heterogenosti ove bolesti. Od 2017. bivaju odobreni novi lekovi za akutnu mijelodnu leukemiju: midostaurin, gilteritinib, CPX351, enasidenib, ivosidenib, venetoclax i glasdegib, dok je ponovo odobrena upotreba gemtuzumab ozogamicina. Savremeno lečenje akutne mijelodne leukemije podrazumeva individualni pristup pacijentima koji se bazira na prognostičkim parametrima kao što su procena genetskomolekularnog rizika prilikom dijagnoze i minimalne rezidualne bolesti određene posle dva primljena ciklusa hemioterapije, sa jedne strane i procena podobnosti samog pacijenta za intenzivnu hemioterapiju na osnovu opšteg funkcionalnog stanja, komorbiditenog indeksa i gerijatrijske procene starijih od 60 godina, sa druge strane. U pogledu lečenja akutne promijelocitne leukemije, kombinacija arsen trioksida i all- trans-retinoične kiseline je prihvaćena kao optimalni tretman standardnog oblika bolesti (leukociti < $10x10^9$/L) dok se za lečenje oblika visokog rizika (leukociti >$10x10^9$/L) i dalje preporučuje kombinacija all-trans-retinoične kiseline i hemioterapije. **Zaključak.** Novi terapijski modaliteti, uz alogenu transplantaciju i uz individualni pristup pacijentu su značano izmeniti ishod akutne mijeloidne leukemije. Poseban izazov u lečenju predstavljaju pacijenti nepodobni za intezivnu hemioterapiju zbog starosti i/ili komorbiditeta i pacijenti sa relapsom/rezistentnom akutnom mijelodnom leukemijom.

Ključne reči: akutna mijeloidna leukemija; terapija; prognoza; procena rizika; ishod lečenja

Introduction

Acute myeloid leukemia (AML) is a rare malignancy with an estimated incidence of 5.06 patients per 100.000 people and with average age of 70 years at diagnosis [1]. Five-year survival of adult AML patients, treated with standard-dose chemotherapy (ChT) and allogenic hematopoietic stem cell transplantation (allo-HSCT), where indicated, was < 30% until recently. However, in patients older than 60 years, five-year survival was < 10% [2, 3]. Due to the striking biological and clinical heterogeneity of AML, no new drugs were introduced in treatment protocols for this disease until 2017. Risk stratification based on cytogenetical and mo-

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Abbreviations

FLT3	– fms-related receptor tyrosine kinase 3
FLT3-ITD	– mutation an internal tandem duplication (ITD)
FLT3-TKD	– mutation in the tyrosine kinase domain
Ara-C	– citarabine
IDH mutations	– mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) genes
Bcl-2	– "B-cell lymphoma-2" cellular protein that inhibits apoptosis
OS	– overall survival
CR/CRi	– complete remission/incomplete remission
FDA	– The United States Food and Drug Administration
EMA	– European Medicines Agency
ELN	– European LeukemiaNet
DLI	– donor lymphocyte infusion

lecular profile of AML at diagnosis [4] and the assessment of minimal residual disease (MRD) [5], allow an individual approach to treatment and the identification of patients suitable for target therapy [6, 7].

Treatment Overview

The introduction of new drugs began from 2017 with: midostaurin - oral multikinase inhibitor registered for the treatment of de novo FLT3$^+$AML adults in addition to the standard-dose ChT; gilteritinib - selective oral AXL receptor kinase inhibitor approved for the treatment of adults with relapsed/refractory (R/R) FLT3-ITD$^+$ AML as a monotherapy; CPX351 - dual-drug liposomal encapsulation of ara-C and daunorubicin with the drug ratio of 5:1 which has been approved for the treatment of adults with therapy-related-AML (t-AML) and AML with myelodysplasia-related cytogenetic changes (MRC-AML); enasidenib and ivosidenib - oral selective inhibitors of mutated IDH1 and IDH2 enzymes approved as a monotherapy for adults with R/R AML; venetoclax - a highly selective Bcl-2 protein inhibitor approved in combination with either hypomethylating agents (HMA) or low-dose ara-C (LDAC) for the treatment of *de novo* AML patients aged ≥ 75 or those with comorbidities that preclude use of intensive induction ChT. Similarly, glasdegib, an oral hedgehog pathway inhibitor, combined with LDAC is approved for patients ≥75 years of age or those who are unfit for induction ChT. Additionally, gemtuzumab ozogamicin has been reintroduced as a treatment option for adults with de novo CD33$^+$ AML, as a monotherapy, or in combination with standard-dose ChT. Moreover, it can be used as a monotherapy for R/R CD33$^+$AML in children older than two years and adults [2]. Allo-HSCT is an essential treatment option for patients with high-risk cytogenetics and molecular profile and patients with measurable MRD after two cycles of high dose ChT [7].

FLT3 inhibitors

One of the most important advances in treatment of de novo FLT3+AML patients is the introduction of midostaurin. Namely, approximately 20% of AML patients express FLT3-ITD which has been associated with early relapse and short OS. Moreover, studies have reported that a higher mutant allelic burden is associated with a worse prognosis. On the other hand, around 10% of AML patients express FLT3-TKD mutation, whose prognostic significance is undetermined. Midostaurin was applied with standard-dose ChT ("3+7" induction, ≤ 4 cycles of consolidation) on days 8 to 21 of a 28-day treatment cycle and, afterward, as monotherapy over 12 months, reducing the rate of mortality by 22% (uncensored for allo-HSCT) compared to the control group, receiving placebo with ChT. Patients who underwent allo-HSCT in the first remission and who received midostaurin before transplantation, had longer remission duration and higher OS compared to the control group [7]. Gliteritinib, as a monotherapy, has been approved for the treatment of R/R FLT3-ITD$^+$ AMLin adults as well [9].

CPX351

CPX351 has been approved for treating adults with *de novo* t-AML and MRC-AML. Both aforementioned types of AML are associated with a very poor prognosis [10]. Results of the study including patients ≥ 60 years diagnosed with t-AML, MRC-AML and secondary AML showed that patients treated with CPX351 had significantly higher OS than those treated with standard-dose ChT (9.56 *vs.* 5.95 months). Moreover, the rate of mortality in patients treated with CPX351 aged 60-69 and 70-75 years was reduced by 32% and 45%, respectively [11].

mIDH inhibitors

Inhibitors of mutant IDH enzymes (mIDH) have contributed significantly to the treatment of AML. Enasidenib is an inhibitor of mIDH2 and ivosidenib is mIDH1 inhibitor. IDH enzyme mutations are present in 20% of AML patients. Namely, in the study which included adults with R/R AML, the use of enasidenib 100 mg daily led to a favorable response in 40% of patients lasting for 5.8 months on average. Additionally, in 19% of patients who achieved CR the duration of the response was 19.7 months (average) [12, 13].

Gemtuzumab-ozogamicin

Gemtuzumab-ozogamicin (GO) was re-approved for the treatment of CD33$^+$ AML. Namely, it was approved as a monotherapy for R/R AML in patients > 60 years in 2000. However, it was withdrawn from the market in 2010 due to adverse events. However, new studies have shown that GO, if administered in lower doses and in fractionated treatment regimens in addition to standard ChT, improves survival rates and prolongs CR, both in older patients with de novo AML and favorable/intermediate risk patients [14]. Therefore, its use is now approved for the treatment of adults with *de novo* CD33$^+$ AML, in combination with standard-dose ChT or as a monotherapy. Moreover, it could be used as a monotherapy in R/R CD33$^+$AML children aged > 2 years and adults [7].

Treatment of unsuitable patients

Novel drugs are also introduced for the treatment of elderly patients who are unsuitable for intensive ChT [15]. The eligibility of patients for ''intensive'' treatment is based on functional status, comorbidities and geriatric assessment of older patients with AML [7]. The current standard therapy for these patients are HMA - azacitidine and decitabine, with a remission rate of 26-28% [4]. FDA approved venetoclax combined with either HMA or LDAC as well as glasdegib with LDAC for the treatment of *de novo* AML patients ≥75 years, unsuitable for intensive ChT. Venetoclax, combined with LDAC or HMA provides CR or CRi in 62-68% of patients. Moreover, the average duration of remission is 11.3 months, while estimated one-year survival rate is 60-72%. The incidence of early death is 2-3% and response time is one month [16]. Glasdegib, combined with LDAC leads to significantly longer survival compared to patients treated with LDAC, only (8.8 *vs*. 4.9 months). Response rate (CR+CRi) was also markedly higher in the glasdegib group (20 *vs*. 4.5%) [17].

Relapsed/refractory AML

Almost 20% of younger and more than 50% of elderly patients do not achieve CR after at least two intensive induction regiments (primarily resistant). Additionally, relapse is registered among 50-70% of patients with AML. The prognosis of R/R AML is highly unfavorable and dependent mainly on the patient's suitability for intensive ChT and allo-HSCT. The 5-year OS for adults with AML after relapse is approximately 10% depending on prognostic factors (age, duration of first CR, cytogenetics at diagnosis, molecular features, and history of prior allo-HCT) [18]. Molecular re-evaluation at relapse is recommended in order to identify patients suitable for targeted salvage options. Thus, in case of relapse, it is advisable to repeat the analysis of the FLT3 gene mutations. Moreover, if the ivosidenib and enasidenib are available in presence of mIDH1/IDH2 should be determined [7]. Recent regulatory agency approval of several novel agents has transformed the treatment of R/R AML. If the AML relapse occurs after the allo-HSCT, especially after six months post-transplantation, secondary HSCT or DLI are recommended. For patients with R/R AML unsuitable for intensive ChT, HMA or LDAC combined with venetoclax, gilteritinib monotherapy for FLT3-ITD/FLT3-TKD positive patients, ivosidenib/enasidenib for mIDH1/IDH2 positive patients, melphalan or palliative/supportive care could be implemented [7].

Treatment of acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is the most malignant form of AML and its treatment is different from other types of AML. The introduction of all-trans-retinoic acid (ATRA) and later arsenic trioxide (ATO) made a revolution in the treatment course and prognosis of APL [19, 20]. Precisely, ATRA induces maturation of APL blasts through a conformational change of the PML–RARA fusion transcripts. This leads to terminal myeloid differentiation of APL blasts and apoptosis [21]. Firstly, ATRA was used as monotherapy in 1987 with excellent results regarding CR achievement. However, relapse rate remained high despite continuous ATRA treatment. That is why anthracyclines with or without cytarabine were reintroduced in APL treatment simultaneously with ATRA. This combination became the standard of care for APL in the nineties [19]. However, the mechanism of action of ATO has not been fully understood. It has been shown that it induces both differentiation and apoptosis of APL blasts [21]. In 2000 ATO was approved as a monotherapy for R/R APL [19]. Later, studies regarding ATO therapy in newly-diagnosed APL patients with or without ATRA were launched. Results of the trials APL0406 and AML17 have shown lower relapse rate and better OS in „ATRA+ATO" arm compared to „ATRA+ChT" arm provided that „ATRA+ATO" (CT-free regimens) has become the standard of care for patients with standard-risk APL [21–23]. For, patients with high-risk APL, optimal treatment is still the subject of debate. According to the latest ELN recommendations, ATO+ATRA could be used in high-risk patients along with idarubicin and GO [24]. However, ATO and GO are not approved by EMA for high risk APL and, for that reason, „ATRA+ChT" is still the standard of care for this group of patients [25, 26].

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