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ANTI-TUMOUR TREATMENT

Emerging treatment strategies for acute myeloid leukemia (AML) in the elderly

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Summary Acute myeloid leukemia (AML) is more prevalent in older adults, with an incidence in the United States of 17.6 per 100,000 for those ⩾65 years of age, compared with an incidence of 1.8 per 100,000 for those <65 years of age. While there have been improvements in survival during the last decade for younger patients, prognosis in elderly patients is still poor; approximately 50% achieve complete responses, but many of them relapse. With increasing age, more patients are suboptimal candidates for standard induction chemotherapy due to poor performance status, pre-existing myelodysplasia, unfavorable cytogenetics, treatment-related AML, multidrug resistance protein expression, and CD34 positivity, which are often characteristic of this patient population. In addition, the presence of comorbid conditions make many treatment options less tolerable for elderly patients. Several investigators have described subgroups showing no benefit after intensive treatment approaches in recent years. However, several novel agents have been developed to treat elderly AML patients. These include new chemotherapeutic agents, such as nucleoside analogs, as well as targeted therapies like farnesyltransferase inhibitors, tyrosine kinase inhibitors, epigenetic drugs, and antibodies. On the other hand new insights into the biology of the disease lead to a better understanding of its heterogeneity. Thus, with a variety of novel substances at hand it is increasingly important to introduce a risk-adapted approach for the optimal management of patients. This review will identify subgroups not likely to benefit from intensive chemotherapy and highlight the efficacy and tolerability of new agents in the treatment of AML.

Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. The majority of patients are >60 years and median age at diagnosis is 65—70 years. While there have been improvements in survival during the last

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decade for younger patients with AML, the prognosis in elderly patients remained poor and although the majority of clinical trials include primarily or exclusively younger individuals, the elderly comprise the larger subgroup, presenting with distinct biological and clinical characteristics.[1,2]

Chemotherapy affects elderly patients different from younger patients. Patients >60 years have a lower complete response (CR) rate after intensive chemotherapy and a much higher relapse rate. AML in the elderly often arises from myelodysplastic syndromes and tends to show a less acute progression compared to de novo AML in younger adults. Good-risk karyotypes, like t(15;17) occur only rarely, while high-risk, especially complex karyotypes, are common as well as overexpression of multidrug resistance (MDR) phenotypes.[3–9] Furthermore, comorbidities are common, leading to an increased early death rate. These differences are best described in a retrospective analysis by Appelbaum et al. on the effect of age in 968 adults with AML treated in five recent Southwest Oncology Group trials performed. The authors found that a poorer performance status, lower white blood cell counts, and a lower percentage of marrow blasts correlate with increased age. Multidrug resistance occurred in 33% of AML patients below the age of 56 as compared to 57% in patients older than 75 years. The percentage of patients with favorable cytogenetics dropped from 17% in those younger than 56 to 4% in those older than 75 years, while the proportion of patients with unfavorable cytogenetics increased from 35% to 51%. The difference in treatment outcome could not only been explained by the higher percentage of poor-risk karyotypes in the elderly patients, but was seen in all cytogenetic risk groups, with the greatest influence of age seen in the intermediate and good-risk subgroups.[10] Thus, elderly patients with AML require different treatment approaches that account for disease biology, performance status, and comorbidities. It is of major importance to define which prognostic subgroups will benefit from intensive treatment regimens and which subgroups will benefit more from supportive care. These latter patients are candidates for novel targeted therapies. Several of these agents have recently entered clinical trials, and some have shown promising results that represent an opportunity for the treatment of this poor-risk subgroup in the future.

Chemotherapeutic approaches in AML and prognostic factors

Intensive combination chemotherapy usually includes cytarabine and anthracyclines (e.g. 3 + 7 schedule), with a CR rate between 45% and 60%. The probability of remaining in remission 3 years after diagnosis is below 10%, the median overall survival (OS) 5–10 months, and the 5-year survival rate 6–12%.[11–13] These already disappointing results are still likely to overestimate the efficacy of chemotherapy in elderly AML patients, as most studies included only patients considered to be medically fit. Attempts have been made to improve induction chemotherapy results by substituting other anthracyclines or structurally different chemotherapeutic drugs (including fludarabine, topotecan, cyclophosphamide, or etoposide) for daunorubicin. The results have mainly been disappointing with regard to OS, but topotecan-cytarabine regimens have demonstrated significantly lower induction mortality rates, suggesting a possible benefit of this combination in elderly patients with AML.[12–15] Additionally, the optimal postremission treatment regimen remains unclear.[7,12,15] The inclusion of novel agents may improve the so far disappointing results seen with maintenance treatment in the future.

Because of the short duration of remission, short survival and the high early mortality rate associated with intensive treatment in the elderly, it is important to assess predictive prognostic factors for outcome. A study by Leith and colleagues ($n = 211$) showed that 32% of patients >55 years of age with AML had unfavorable cytogenetics and 71% had overexpression of MDR1, which was associated with a CR rate of 12% in this subgroup.[8] Recently, our group reported data on the unfavorable effect of abnormal cytogenetics on treatment outcome with intensive chemotherapy in 146 patients with AML and high-risk MDS (Table 1).[16] Other investigators have found similar results.[13,17]

Although cytogenetic status is the most important prognostic factor for elderly patients with AML, several factors can contribute to the poor-prognosis: age $\geqslant$70–75 years, poor performance status, pre-existing myelodysplastic or myeloproliferative disorders, treatment-related leukemia, CD34 positivity, elevated serum lactate dehydrogenase ($\geqslant 2 \times$ upper limit of normal), leukocytosis ($\geqslant 100 \times 10^9$/L), thrombocytopenia ($\leqslant 20 \times 10^9$/L), and existence of comorbidities.[9,13,17–21] Kantarjian and colleagues recently suggested a predictive model including age $\geqslant$75 years, unfavorable karyotype, poor performance status, longer duration of antecedent hematologic disorder, treatment outside the laminar airflow room, and abnormal organ function as poor prognostic factors. CR rates, induction mortality and 1-year survival according to the proposed risk groups are shown in Table 2.[13]

Table 1 CR rate and OS in elderly patients treated with intensive chemotherapy according to cytogenetic abnormalities

Karyotype	CR rate (%)	Overall survival (median)
Overall $n = 146$	56	9.5 mo
Normal $n = 78$	70	18 mo
Abnormal, noncomplex $n = 36$	69	6 mo
Abnormal, complex $n = 32$	46	4 mo

Table 2 CR rate, induction mortality, and 1-year survival according to a proposed score for elderly patients receiving intensive chemotherapy[12]

Risk group	CR rate (%)	Induction mortality (%)	1-year survival (%)
Favorable-risk	60	10	>50
Intermediate-risk	50	30	30
Unfavorable-risk	<20	>50	<10