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Brief communication

Amsacrine containing induction therapy in elderly AML patients: Comparison to standard induction regimens in a matched-pair analysis

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Abstract

Many elderly patients with newly diagnosed acute myeloid leukemia (AML) present with cardiac comorbidity precluding the use of anthracycline containing chemotherapy regimens. Amsacrine, a topoisomerase II inhibitor, has been proposed as possible alternative to anthracyclines. Here, we report about the combination of amsacrine (210 mg/m^2), in replacement for daunorubicin (DNR), with standard dose cytarabine and thioguanine (TAA) to elderly patients (≥60 years of age) with impaired cardiac function. The outcome of 16 patients with a median age of 66 years treated between 1997 and 2003 was compared with standard treatment regimens of the AMLCG study group in a matched-pair analysis. There were no statistically significant differences in response rate, relapse free survival or overall survival between TAA treated patients or standard therapy. In conclusion, replacing anthracyclines with amsacrine for induction therapy of AML patients with significant cardiac comorbidities represents a treatment option without compromising the potential curability of the disease.
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Keywords: Amsacrine; AML; Induction therapy

1. Introduction

Treating older patients with AML continues to be an important challenge. While the age group of 60 years and older represent only one third of the patients included in large multicenter studies they actually account for the majority of AML patients [1]. The unfavorable biology of this disease in the elderly and the increased incidence of relevant comorbidities resulting in increased toxicity and/or less intensive chemotherapy regimens are among the reasons for the poor prognosis in this age group [2]. Previous studies clearly demonstrated dose related therapeutic effects in elderly AML patients over 60 years, in particular for daunorubicin (DNR), in both induction and post-remission therapy [1]. However, many elderly patients present with significant cardiac comorbidity precluding the use of anthracyclines. The acridine derivative *m*-amsacrine (AMSA), a topoisomerase II inhibitor, has been proposed as substitute for anthracylines in such cases [3]. The cardiac toxicity of AMSA has been reported to be significantly less common than for anthracyclines and only occurred in association with low serum values for potassium or magnesium [3].

However, it is not clear to date whether induction therapy regimens containing AMSA instead of anthracyclines display similar antileukemic efficacy in AML patients.

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2. Materials and methods

Standard therapy was applied according to the German AML Cooperative Group 1999 protocol for elderly patients ≥60 years of age as follows: induction therapy consisted of either a combination of 6-thioguanine (200 mg/m^2, days 3–9) with cytarabine (100 mg/m^2/24 h, days 1–2 and 100 mg/m^2, q12 h, days 3–8) and DNR (60 mg/m^2, days 3–5) (TAD) or high dose cytarabine (1 g/m^2, q12 h, days 1–3) with mitoxantrone (10 mg/m^2, days 3–5) (HAM). A second induction course consisting of HAM starting on day 22 was applied in patients who did not reach complete blast clearance on day 16 [1]. Complete remission (CR) was defined by a bone marrow blast count of less than 5%, absence of leukemic blasts in peripheral blood smears, resolution of extramedullar leukemic infiltrates, peripheral leukocyte counts above $1.5 \times 10^9\,l^{-1}$ and platelet counts above $100 \times 10^9\,l^{-1}$. Patients achieving a CR upon induction received a TAD consolidation therapy and scheduled maintenance therapy over 3 years with cytarabine/DNR (AD), cytarabine/6-thioguanine (AT) and cytarabine/cyclophosphamide (AC) alternating every month. In patients with contraindications against cardiotoxic substances such as congestive heart failure (New York Heart Association stage III–IV) or significant decreased left ventricular systolic function (shortening fraction below 30% and/or ejection fraction below 40%) due to previous myocardial infarction, DNR was replaced by AMSA (210 mg/m^2, days 3–5) for induction and consolidation cycles (TAA) as well as for maintenance therapy leaving the remaining treatment algorithm unchanged.

The outcome of 16 patients with a median age of 66 years treated in our department with AMSA instead of DNR between 1997 and 2003 was compared with the standard treatment regimens of the AMLCG study group in a matched-pair analysis. In earlier analyses age, cytogenetics, serum lactate dehydrogenase (LDH) and white blood cell count (WBC) at the time of diagnosis were identified as independent prognostic factors [1]. Therefore, patients were matched for these variables and for AML subtype according to the French–American–British (FAB) classification (see Table 1). Cytogenetic subgroups were defined as previously suggested and were regarded at highest priority to find matched pairs [4]. Toxicity, early death rate within the first 4 weeks after diagnosis, remission rate after induction, relapse free survival (RFS) as well as overall survival (OS) were compared. Statistical analysis was performed with the non-parametric Mann–Whitney test. Survival times were compared with the log-rank test. All displayed p values are two-sided.

Table 1
Patient characteristics and results (values are presented as medians and standard error, if not stated otherwise)

	TAA	AMLCG (10 HAM; 6 TAD)
No. of patients	16	16
Age (years)	66.5 ± 5.6	66 ± 5.1
Gender (male/female)	14/2	10/6
FAB subtype	M0 (n = 2) M1 (n = 1) M2 (n = 4) M4 (n = 2) M5 (n = 3) M6 (n = 3) M7 (n = 1)	
Cytogenetics[a]	Intermediate (n = 7) Unfavorable (n = 8) Favorable (n = 1)	
LDH (U/l)		
>600	6/16 (37.5%)	6/16 (37.5%)
<600	10/16 (62.5%)	10/16 (62.5%)
Median	618 ± 341 p = 0.468	351 ± 123
WBC ($\times 10^3\,\mu l^{-1}$)		
>20	10/16 (62.5%)	10/16 (62.5%)
<20	6/16 (37.5%)	6/16 (37.5%)
Median	40.1 ± 24.6 p = 0.696	24.5 ± 13.1
Early blast clearance (<5% day 16)	8/16 (50%)	9/16 (56.25%)
CR	9/16 (56.25%)	5/16 (31.25%)
RFS (months)	32 ± 8.4 p = 0.797	32 ± 15.1
Long-term CR (≥3 years)[b]	3/16 (18.75%)	2/16 (12.5%)
Early death	1/16 (6.25%)	2/16 (12.5%)
OS (months)	16 ± 6.1 p = 0.197	8.5 ± 5.3

Abbreviations—TAA: thioguanine, cytarabine, and amsacrine; AMLCG: acute myeloid leukemia cooperative study group; LDH: lactate dehydrogenase; WBC: white blood cell count; CR: complete remission; RFS: relapse free survival; OS: overall survival.

[a] Favorable karyotypes included t(8;21)(q22;22), inv(16)(p13q22), or t(16;16)(p13;q22). Unfavorable caryatides included losses or deletions of chromosomes 5 or 7 (−5, 5q−, −7, 7q−), chromosome 3(q21q26) abnormalities, abnormal chromosome 11(q23), or complex aberrant karyotypes with at least three structural and/or numerical abnormalities. Intermediate karyotypes were defined by normal karyotype or abnormalities not considered favorable or unfavorable.

[b] Three-year survival probability in the whole AMLCG study population for patients of 60 years and older (n = 960) 18% for TAD-HAM and 19% for HAM-HAM induction therapy [1].

3. Results and discussion

There were 32 patients available for analysis with a median age of 66 years (range, 56–78 years). Matched pairs were comparable for age, FAB subtype, cytogenetics, WBC and LDH at time of diagnosis and representative in terms of these risk factors for the whole AMLCG study population of this age (detailed patient characteristics, see Table 1). In the comparator group 10 patients received HAM, 6 TAD as first induction cycle. Short- and long-term toxicities in both groups were tolerable and within the reported range for the AMLCG study group [1] (data not shown). One early death occurred in the TAA group versus two early deaths in the

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