Clinical Characteristics and Treatment Outcome of Hypocellular Acute Myeloid Leukemia Based on WHO Classification

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Abstract The hypocellular acute leukemia is very rare atypical leukemia with frequency of 5–7% among patients with acute leukemias. It mainly occurs in older patients and usually has a myeloid phenotype. It is still unclear whether the outcome of hypocellular acute myeloid leukemia is less favorable than adult acute myeloid leukemia with normal cellularity. We retrospectively analyzed all hypocellular acute myeloid leukemias which were treated in 16 years period, between January 1998 and December 2014. There were 33 patients, 21 male and 12 female. The median age of the patients was 58.9 years (ranging from 19 to 88 years) and median cellularity of bone marrow was 16%. All patients presented with cytopenias with median white blood cell count $1.9 \times 10^9/l$, platelets $47.2 \times 10^9/l$ and hemoglobin 85.9 g/l. Nineteen patients were treated with standard 3 + 7 protocol (daunoblastin 45 mg/m^2 1, 3, 5 days, cytosin-arabinozide $100 \text{ mg/m}^2/12 \text{ h}$ for 7 days), 5 patients with HDAC protocol and, 3 (9%) with low dose cytosin-arabinoside and in 6 (18.1%) patients only supportive therapy was applied. One patient died on 34 day after treatment with HiDAC, 3 patients after treatment with 3 + 7 regimen in full doses on days 23, 35, and 58 days. Complete remission was achieved in 20/33 (60.60%) patients, with median duration of 14 months. Median overall survival (OS) of the entire cohort was 16 months,

and for the treated group 21 months (range 5–67 months). Median OS of patients treated with low dose cytosine-arabinoside was 6 months. The advanced age ($p = 0.009$, $\text{KK} = -0.46$, Log rank, $p = 0.031$) as well as therapy options (Log rank $p < 0.0001$) shows a significant correlation with OS. We report a cohort of patients with hypocellular acute myeloid leukemia who responded to standard induction chemotherapy as are in standard acute myeloid leukemia.

Keywords Age · Hypocellular acute myeloid leukemia · Treatment · Prognosis

Introduction

Hypocellular acute myeloid leukemia (AML) is an atypical leukemia, characterized by hypocellular bone marrow and with $\geq 20\%$ blasts affecting more frequently elderly patients [1, 2]. In children hypocellular acute lymphoblastic leukemia has been described [3]. These patients have a relatively low tumor burden, and disease may have a less aggressive course [1, 2]. Complete remission may be achieved with standard induction treatment protocols following intensive supportive care which enables to survive the period of aplasia with less morbidity and mortality [1]. In earlier reports hypocellular bone marrow was defined as less than 40% or even 50% cellularity but currently hypocellular bone marrow is considered as less than 20% cellularity [1, 2, 4]. In some cases the diagnosis is difficult because some features of hypocellular AML are similar to hypocellular myelodysplastic syndrome or aplastic anemia, and blasts are scattered in extremely low bone marrow cellularity so that the enumeration is difficult. In order to facilitate the diagnosis Bennet and Orazi have proposed

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guidelines for differential diagnosis between these entities [4].

Materials and methods

The diagnosis of AML was based on morphological, cytochemical, immunophenotypic and cytogenetic analyses of bone marrow aspirate and core biopsies and was subtyped according to new WHO classification of myeloid neoplasms [5]. Bone marrow (BM) and peripheral blood (PB) were stained with May-Grunwald-Giemsa and cytochemical analyses were made with peroxidase (POX), Sudan black B (SBB) and periodic acid-Schiff (PAS). The immunophenotype profile was established in 19 patients using mononuclear cells from the bone marrow aspirates. The cell surface antigen patterns were determined by direct immunofluorescence. Antigenic expression of the leukemic cells was analyzed by flow cytometry on a FACS Calibur flow cytometer (Becton–Dickinson, USA) with a commercial panel of monoclonal antibodies as described previously [6]. Cytogenetic analyses were performed on unstimulated bone marrow cells by direct preparation and following 24 h of culture in RPMI 1540 culture medium with 25% fetal calf serum at 37 °C as previously reported [7]. The karyotype was assayed according to the depictions and descriptions given in the International System for Human Cytogenetic Nomenclature 2009 [8]. The performance status was evaluated according to the ECOG system [9]. The patients signed an informed consent and were treated according to Declaration of Helsinki.

Statistical methods

The study utilized the Mann–Whitney *U* test for non-parametric data. Survival was analyzed using the Kaplan–Meier log rank-test.

Results

A retrospective analysis was made of all patients with hypocellular AML diagnosed at the Clinic of Hematology, University Clinical Center of Serbia, from January 1998 until December 2014. Our series comprised 33 patients, 21 (63.6%) male and 12 (36.3%) female.

The characteristics of the patients are presented in Table 1. The median age of the patients was 58.9 years (range 19–88 years). The median white blood cell count (WBC) was $1.8 \times 10^9/l$ (range 0.3–2.0), platelets $47.2 \times 10^9/l$ (range 9–72), hemoglobin (Hb) 85.9 g/l (range 60–111).

Table 1 Patient characteristic at diagnosis

Variables	N (%) / median (range)
Gender	
Male	21 (63.6%)
Female	12 (36.3%)
Age (years)	58.9 (19–88)
Blood counts at diagnosis	
Hemoglobin (g/L)	85.9 (60–110)
Platelet ($\times 10^9/L$)	47.2 (9–72)
TWBC ($\times 10^9/L$)	1.8 (0.3–2.0)
Blasts in PBS ^a	2 (1–14)
Bone marrow cellularity (%)	14.7 (3.5–19.7)
Bone marrow blast (%)	28 (12–42)
LDH (U/L)	621.5 (320–1201)
Cytogenetic risk group ^b	
Standard	15 (45.45%)
Intermediate	8 (24.24%)
High risk	1 (3.03%)
Not done	9 (27.27%)
ECOG-Score	
0	6 (18.2%)
1	16 (48.5%)
2	10 (30.3%)
3	1 (3.0%)
Specific comorbidity index 0	25 (75.75%)
Specific comorbidity index 1	8 (24.25%)
Types of AML (morphologic)	
AML with minimal differentiation	5 (15%)
AML without maturation	13 (39.39%)
AML with maturation	8 (24.24%)
Acute myelomonocytic leukemia	1 (3.0%)
Acute monoblastic leukemia	2 (6.0%)
Pure erythroid leukemia	0 (0%)
Acute megakaryoblastic leukemia	1 (3.0%)
Unclassified	3 (9.0%)

^aPB peripheral blood smear

^bCytogenetic risk group

In two patients myelodysplastic syndrome as antecedent disorder was found. No one of presented patients received prior chemoradiotherapy. Only two patients had signs of tissue infiltration manifested as hepatomegaly and two patients had splenomegaly. No patients had lymphadenopathy and only three patients had mild hemorrhagic syndrome as petechiae and skin hematomas.

Only one patient (3%) had an Eastern Co-operative Oncology Group performance status of 3. The majority patients ($n = 26$) were in good physical condition with an ECOG-PS 0 and 1. Seven patients had circulating blasts in peripheral blood ranging from 4 to 15% (median 2%).

Median leukocyte count was $1.8 \times 10^9/l$ (range 1.2–2.2) and none had leucocytosis. Cytogenetic analysis was not performed in 9 patients, normal karyotype was found in 15 patients, and 8 patients had intermediate II karyotype, one patient showed deletion of chromosome 7. The distribution of morphologic subtypes according to WHO classification revealed the following AML subtypes: AML with minimal differentiation 5 (15%), AML without maturation 13 (39.39%), AML with maturation 8 (24.24%), acute myelomonocytic leukemia 1 (3.0%), acute monoblastic leukemia 2 (6.0%), acute megakaryoblastic leukemia 1 (3.0%), unclassified 3 (9.0%). AML without maturation according to WHO classification was the most common subtype, accounting for 39.39% of all cases, followed by AML with maturation and AML with minimal differentiation with the incidence of 8% and 5% respectively (Table 2) [5].

Nineteen patients received 3 + 7 regimen (cytarabine in dose 200 mg/m² daily as a continuous I.V. infusion on days 1–7, and Daunoblastine in dose 45 mg/m²/day on 3 consecutive days), 5 patients received high dose cytarabine-based regimen-HiDAC, 3 (9%) patients received low dose cytosine-arabinoside and in 6/33(18.1%) patients received supportive care (Table 2). The distribution of treatment of this cohort of patients are similar to the regimens applied in elderly patients with AML in our institution previously reported [10].

The CR in this group of patients is 60.6% (20/33), and among those who received treatment is 83.3%. From those chemotherapy treated patients including patients treated with 3 + 7 regimen, HiDAC and low dose cytosin arabinoside. In 14 patients in the period of aplasia G-CSF was applied. The median period of neutropenia and thrombocytopenia was 18 days (range 10–34 days). In one patient after HiDAC aplasia lasted 34 days, after which period he finally died.

The median duration of CR was 14 months. The median OS for the whole group was 16 months and for the treated patients 21 months. The longest survival had the patients treated with HDAC and bone marrow transplantation.

Discussion

Hypocellular AML is characterized by pancytopenia and bone marrow hypocellularity with equal to or more than 20% blast along with the absence of tumor masses or tissue infiltrates (1.4). In some earlier reports, cellularity < 40% or 50% was considered as hypocellular [2, 11–15]. This atypical entity is diagnosed more frequently in older patients. Hypocellular acute lymphoblastic leukemia occur in children and young persons [3]. There are limited information's on clinical, laboratory and prognostic parameters of hypocellular AML what makes recommendations for managing this entity difficult specially regarding the fact that it is seen more frequently in older patients. As the treatment of the elderly with hypocellular leukemia is complicated, it may be possible to use some of the stratification parameters used for intensive therapy versus those that should be treated with standard therapy or supportive care.

A better understanding of characteristics of hypocellular AML may allow for a more individualized therapeutic approach although the ultimate decision as to whether to give standard chemotherapy or palliation very much depends on patient's compliance (age, ECOG PS and comorbidities) and dedication of the physician. One must also bear in mind that hypocellular AML is the disease of elder age group but an extension of OS by several months or even years seems precious from the standpoint of a patient.

The frequency of hypocellular AML was reported to be 5–7% of all AML patients but according to new recommendations regarding marrow cellularity when restricts to less than 20% the true frequency could be even lower [1, 2, 12]. The marrow hypocellularity is the reason for difficulties in differentiating this syndrome from hypocellular myelodysplastic syndromes and aplastic anemia. Bennet and Orazi have proposed guidelines to facilitate the differential diagnosis between this diseases, including counting differential of 100 cells in peripheral blood, differential 500 cells from bone marrow aspirate, iron staining and immune staining of bone marrow biopsy for CD34/CD117 markers to determine presence of immature precursors (ALIP), flow cytometry findings and cytogenetics [4].

Table 2 Treatment and outcomes of the patients

Treatment received	N (%)	Outcome CR ^a N (%)	OS Median (range)
3 + 7 Induction	19/33 (48%)	16/33 (48.48%)	27 (2–42)
HDAC	5/33 (15.1%)	4/33 (12.12%)	47 (25–67)
No treatment/Supportive	6/33 (18.1%)	0 (0%)	13 (3–26)

^aCR complete remission, OS overall survival

The pathogenesis of hypocellularity is unclear whether the leukemia is secondary to the hypocellularity or if it is the primary event. It has been suggested that leukemia cell populations inhibit myelopoiesis through a humoral mechanism [14]. Also important consideration is that myeloid precursors in older patients had an increased susceptibility to the different inhibitors [4, 15]. These patients have a lower leukemic burden and experience a more indolent course and can commonly achieve a good response to remission induction therapy what we have shown in our group of patients. All our patients fulfilled diagnostic criteria with pancytopenia in peripheral blood, bone marrow cellularity equal or less < 20% and more than 20% of blast cells in bone marrow. In our study population, only one patient was diagnosed to have acute myelomonocytic leukemia and none had acute pure erythroid leukemia, which is in contrast to previous reports where these entities were noted to be more frequent [10, 15]. Seventeen (51.5%) of our patients had bone marrow blast percentage between 20 and 28% indicating low tumor burden.

Small percentage of bone marrow blasts may be misdiagnosed as myelodysplastic syndrome but additional counting and staining bone marrow biopsy with CD34 enables more precise enumeration.

Sixteen of our patients were older than 60 years, with median age of 58.9 years. The youngest male patient was 32 years old and had acute myeloblastic leukemia with maturation, with unfavorable cytogenetic finding 46,XY,(-7)(q21). He was treated with HDAC and allogeneic bone marrow transplantation and he is still alive after 65 months. There are many case reports and case series in the literature with experience suggesting that patients with hypocellular AML experience more indolent course and can achieve a good response to standard induction remission chemotherapy [2, 11, 12]. In our group of patients 83.3% achieved CR, 16 with standard 3 + 7 protocol and 4 with HDAC protocol and none treated with low dose cytosine-arabioside so the CR in treated group was 69.6% what is similar to other studies [1]. CR in our chemotherapy treated group was high because treatment was applied in patients with good performance status and in the whole cohort there were no patients with monosomal karyotype (1). The median OS for all patients with hypocellular AML was 16 months (2–67 months) for patients treated with 3 + 7 protocol was similar and for patients treated with HDAC 47 months (25–67 months). OS was significantly influenced by age of the patients ($p = 0.009$, KK = -0.46, Kaplan–Meier Log rank $p = 0.031$ with border line on 55 years, $p < 0.0001$) (Fig. 1).

The other significant factor for OS was treatment. Patients treated with standard 3 + 7 protocol survived significantly better than patients treated with palliative

Fig. 1 Overall patients survival according patients age (survival expressed in months)

therapy and support (Fig. 2). The patients who were treated with chemotherapy live statistically significant longer in comparison with group treated only by supportive measures (Kaplan–Meier Log rank, $p < 0.0001$ (Fig. 2). The treatment significantly correlates with OS ($p < 0.008$). The number of platelets, WBC and LDH, organomegaly did not influence OS.

In older patients the CR was rarely achieved (Mann Withney U test, $Z = -2.55$; $p = 0.01704$). Older patients also had lower number of WBC (KK = -0.37, $p = 0.045$).

In most of the patients the disease has a prolonged indolent course but the disease may take aggressive course and with fatal termination as we experienced in 4 our patients aged 60, 74, 72 and 72 years.

Conclusion. We described a cohort of 33 patients with hypocellular acute myeloid leukemia which is

Fig. 2 Overall survival of patients based on treatment status

characterized by pancytopenia in peripheral blood and low bone marrow cellularity. The frequency of remissions and overall survival were not significantly different from non-hypocellular AML. We argue that this type of leukemia should be treated as non-hypocellular acute myeloid leukemia as they do not have dismal prognosis and may achieve prolonged survival. The long term outcome remains challenging in hypocellular AML.

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Compliance with Ethical Standards

Conflict of interest We declare that there is no conflict of interest.

Human and Animal Rights This article does not contain any studies with animals performed by any of the authors.

Informed Consent The patients signed an informed consent and were treated according to Declaration of Helsinki.

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