Acute promyelocytic leukemia successfully treated also in elderly patients with significant comorbidities: a 20-year single-center experience

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Acute promyelocytic leukemia is a unique entity among acute leukemias. Introduction of all-*trans* retinoic acid and, subsequently, arsenic trioxide in its treatment has markedly improved treatment outcomes for this once frequently fatal disease. Improved outcomes have also been observed in elderly patients, including those in whom standard intensive therapy is contraindicated because of comorbidities.

In our center, a total of 60 APL patients were treated in 1993-2013, of whom 9 were aged 60 or more years. Although most of them had significant comorbidities at the time of diagnosis, eight achieved complete remission. At the time of the analysis, six patients were alive and in long-term remission; two patients died of causes other than APL. The median follow-up was 59 months.

Included is case report of a patient with a high comorbidity score whose treatment was markedly reduced and individualized.

Our experience shows that, in APL patients a curative approach is generally tolerated and should always be attempted regardless of age and comorbidities.

Key words: APL – elderly patients – comorbidity

Acute promyelocytic leukemia (APL) is a unique entity among acute myeloid leukemias (AML). It is characterized by specific genetic (t(15;17)(q22;q21) and the PML/RARα fusion gene in 99% of cases), morphological (M3/M3v) and clinical (coagulation abnormalities with a high risk of fatal bleeding) aspects requiring specific treatment approaches [1-4]. APL accounts for 5-15% of AML cases [5,6]. Addition of all-*trans* retinoic acid (ATRA) to anthracycline-based chemotherapy more than doubled the rates of complete remission (CR), significantly improved overall survival and disease-free survival in APL patients; today, approximately 70-80% of patients may be cured [7,8]. Introduction of arsenic trioxide (ATO)(2007), a drug even more effective than ATRA, has continued to improve the potential of current therapy of the condition [9].

Given the highly effective current therapy and the fatal course of the disease within a short period of time if it is not initiated, ATRA is immediately administered to all patients irrespective of their age. Further therapy is either based on standard protocols or, in case of a severe previous comorbidity, reduced adequately and tailored to a particular patient.

Patients and methods

In our center, ATRA has been available for treating APL for over 20 years. Between February 1993 and the end of 2013, a total of 60 patients were treated, of whom 9 were aged 60 or more years on treatment initiation. The objective of the study was to retrospectively assess the treatment success rate and experience with treatment individualization in this subgroup of patients.

The entire group comprised 60 patients (34 males and 26 females), with ages ranging from 19 to 73 years (median, 43.5 years; mean 45.2 years). In all patients' leukemic promyelocytes, the t(15;17)(q22;q21) translocation and the PML/RARα fusion gene were confirmed. Hypergranular morphology of the tumor cells was noted in 57 patients; three patients had

the microgranular variant (M3v) of the disease. According to a predictive model by Sanz et al. [10], 17 patients (28.3%) were in a low-risk group, 33 (55%) were in an intermediate-risk group and 10 (16.7%) were in a high-risk group. Fifty-six patients had no previous cytotoxic therapy in their history; four patients were diagnosed as having leukemia secondary to earlier chemotherapy or radiotherapy for other malignancies.

The 60+ subgroup consisted of 7 males and 2 females. Six patients were in the "very elderly" category, that is, older than 65 years; three patients were older than 70 years of age. In the subgroup, the median and mean ages were 67.9 and 67.1 years, respectively. Based on the Sanz score, 3 patients were low-risk, 4 patients were intermediate-risk and 1 patient had a high risk of the disease. With respect to the pathogenesis, the disease was defined as secondary in 2 cases. One was that of a 60-year-old female successfully treated (hysterectomy, radiotherapy) for cervical cancer 5 years before being diagnosed with APL. The other was a 61-year-old male who had been followed and repeatedly treated with chemotherapy for peripheral T cell non-Hodgkin's lymphoma (T-NHL) in our center prior to the diagnosis of APL. All patients had the classical hypergranular morphological variant of APL.

For a retrospective assessment of comorbidities, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) by Sorror et al. was used [11]. According to the index, patients with score 0 had a low risk, those with scores 1 and 2 had an intermediate risk and patients scoring 3 or more were in a high-risk group. In our group, three patients scored 0, two scored 3, three scored 4 and one patient scored 8. The median score was 3, that is, suggesting a high risk.

All patients were treated with a combination of ATRA and anthracyclines. The treatment protocols varied with respect to the time periods of treatment of individual patients. The first patient in the 60+ subgroup was treated from 1994. Induction therapy with ATRA + idarubicin was followed by 2 cycles of consolidation therapy (7+3 and 5+2 with daunorubicin) and two-year maintenance therapy with ATRA + 6-mercaptopurine (6-MP) + methotrexate (MTX). Another 4 patients, diagnosed in 1999-2005, were treated according to the GIMEMA protocol (Table 1) irrespective of their Sanz scores.

Three patients diagnosed after 2008 were treated according to the PETHEMA protocol (Table 2). Treatment of one of these patients (male, 70 years) was dramatically reduced due to complications after non-reduced induction therapy. After remission was achieved and the patient was discharged from hospital, pseudomembranous colitis developed with subsequent multiorgan failure requiring long-term hospital stay that postponed consolidation chemotherapy. As late as 5 months after initiation of induction therapy, bridging therapy with ATRA was started (without chemotherapy, four 2-week cycles followed by 2-week pauses) and as late as 9 months from the initiation of induction, consolidation therapy was started, with anthracycline doses reduced to 50%.

The last patient, diagnosed in 2012, has received individualized therapy as described in a case report below.

All patients underwent maintenance therapy.

Results

Out of the 9 patients, eight (89%) achieved CR. Only one patient died of intracranial hemorrhage 3 days after the diagnosis of APL was made. The bleeding had occurred prior to his admission to our center. This was the only patient with leukocytosis at the time of diagnosis; therefore, he was classified as having a high risk according to Sanz et al. and his HCT-CI score was 4.

Table 1. Protocol for treatment of APL according to the GIMEMA/EORTC 06952

Induction:	ATRA 45 mg/m^2 daily in 2 doses until hematologic remission is achieved + idarubicin 12 mg/m^2 daily on days 2, 4, 6 and 8
1st consolidation:	cytosine arabinoside 1g/m^2 once daily + idarubicin 5 mg/m^2 once daily (4 days)
2nd consolidation:	mitoxantrone 10 mg/m^2 once daily + etoposide 100 mg/m^2 once daily (5 days)
3rd consolidation:	cytosine arabinoside 150 mg/m^2/8 hours s.c. (5 days) + idarubicin 12 mg/m^2 once daily (day 1) + 6-thioguanine 70 mg/m^2 three times daily (5 days)
Maintenance:	2 years of ATRA (15 days every 3 months) +/- MTX +/- 6-MP

Table 2. Protocol for treatment of APL according to the PETHEMA LPA 99

Induction:	ATRA 45 mg/m^2 daily in 2 doses until hematologic remission is achieved + idarubicin 12 mg/m^2 daily on days 2, 4, 6 and 8
1st consolidation:	low risk: idarubicin 5 mg/m^2 once daily (4 days) intermediate+high risk: idarubicin 7 mg/m^2 once daily (4 days) + ATRA 45 mg/m^2 (15 days)
2nd consolidation:	low risk: mitoxantrone 10 mg/m^2 once daily (5 days) intermediate+high risk: mitoxantrone 10 mg/m^2 once daily (5 days) + ATRA 45 mg/m^2 (15 days)
3rd consolidation:	low risk: idarubicin 12 mg/m^2 (1 day) intermediate+high risk: idarubicin 12 mg/m^2 (2 days) + ATRA 45 mg/m^2 (15 days)
Maintenance:	2 years of ATRA (15 days every 3 months) + MTX + 6-MP

Of the 8 patients who achieved remission, six were alive at the time of the analysis; then, their median follow-up was 59 months. At 28 months from the diagnosis of APL, one patient with secondary PML died of relapse and progression of primary peripheral T-NHL (initial HCT-CI =3) being in long-term molecular remission of APL. Another patient (initial HCT-CI=4) died 17 years after the diagnosis of APL, in the remission of leukemia as well. The cause of death was acute myocardial infarction (in a patient with chronic ischemic heart disease).

Case report. A 73-year-old male was admitted for dyspnea to a department of internal medicine in June 2012. He was diagnosed with acute pulmonary embolism and anticoagulation therapy was started without the cause for embolism being found. Laboratory tests revealed bicytopenia. As bone marrow cytology was suggestive of APL the patient was referred to our center. There, the diagnosis of PML/RARα-positive APL was confirmed. The initial blood count showed hemoglobin 121 g/L, white blood cell (WBC) count 1.0×10^9/L and platelets 79×10^9/L (without previous substitution). Thus, the patient was categorized as having a low risk according to the Sanz score. However, his comorbidities were of great significance as he was very obese (body mass index = 39), having a history of chronic ischemic heart disease, acute transmural inferior wall myocardial infarction, severe left ventricular systolic dysfunction with an ejection fraction of 30%, combined valve disease, surgical aortic valve replacement with a bioprosthesis, paroxysmal ventricular fibrillation and a prolonged QT interval. Other comorbidities included grade III chronic venous insufficiency of the lower limbs, venous ulcers of the right distal leg and gout involving the first metatarsophalangeal joints. Therefore, the HCT-CI was 8. On admission, the patient's Karnofsky score [12] assessing his general condition was 50. Immediately after hospital admission, ATRA therapy was initiated with standard doses. Given the cardiac comorbidities, standard treatment with idarubicin was contraindicated. ATO was not administered immediately to avoid further prolongation of the QT interval. Due to a high WBC count (24.7×10^9/L and a doubling time of 24 hours) caused by differentiation effects of ATRA and incipient signs of differentiation syndrome, a single 10-mg idarubicin dose was administered on day 15. Subsequently, after the patient was provided with a temporary pacemaker, ten ATO doses of 10 mg/day were administered. After 34 days of his hospital stay, the patient was discharged to outpatient care and continued with ATRA therapy. On day 45 from initiation of the therapy, sternal puncture was performed that confirmed complete hematologic remission, with persisting PML/RARα-positive disease shown by qualitative PCR in both peripheral blood and bone marrow. Induction therapy with ATRA was continued. After therapeutic options were discussed with the patient preferring only outpatient treatment, maintenance therapy with ATRA + 6-MP + MTX was started on day 82 from the diagnosis. Another PCR analysis of PML/RARα after 26 days of maintenance therapy (day 108

from the diagnosis) yielded negative results. Also 3 other tests using peripheral blood (sternal puncture was refused by the patient) were negative. At the same time, his blood count was normal and overall health status was very good. The patient continues with maintenance therapy.

Discussion

AML is a disease of the elderly, with the patients' median age being 65-70 years. In the vast majority of patients over 65 years of age, AML is incurable due to a high frequency of unfavorable cytogenetic changes in tumor cells, primarily resistant diseases and unacceptable toxicity of intensive chemotherapy caused by comorbidities. Long-term survival is achieved in only approximately 10% of patients older than 65 years [13,14].

The age distribution of APL patients is different from that in other forms of AML. The patients' median age is approximately 40-45 years, that is, significantly lower than in patients with other AMLs [15-18]. The disease is rare in children under 10 years of age. Later, the incidence increases, reaches a plateau in early adulthood and remains constant until it decreases after the age of 60 [8]. According to other literature data, however, the incidence remains constant with increasing age [19] or even rises [20-23]. Unlike in other AML subtypes, the increase is not exponential.

The higher age of APL patients is, together with leukocytosis and poorer performance status, considered a primary adverse prognostic factor. Although the effectiveness of treatment of elderly APL patients is no lower than in younger individuals (sensitivity to treatment is the same), there are more early deaths (bleeding) and deaths in remission due to treatment-related toxicity [8].

In our center, basic diagnostic and treatment data from all APL patients have been studied, starting from the first patient receiving ATRA and including patients dying early from bleeding complications. This is a complete unselected group of patients that reflects long-term experience of more than 20 years.

The median age of patients in the reported group, that is, 43.5 years, is consistent with the literature data. The 60-70 age group comprised 6 patients (10%); three patients (5%) were older than 70 years.

CR was achieved in 89% of the elderly patients; the early death (ED) rate was 11%. There were no treatment-related deaths and none of the patients have relapsed thus far. The patients' basic characteristics are shown in Table 3.

The treatment outcomes in the elderly were comparable with those in younger patients (Figure 1), with CR being achieved in 54 out of 60 patients (90%); six patients (10%) died early and 5 patients (10%) relapsed.

Future relapses cannot be ruled out in patients with reduced/individualized therapy. So far, the follow-up has been too short to prove that such adapted therapy may lead to long-term remission. However, it is almost certain that with-

out this treatment, patients' survival would be very short and full-dose therapy would be associated with severe, most likely fatal, complications.

In two recent reviews [5,24] on the management of APL in the elderly, the authors comment on the available published data from both unselected population studies and multicenter clinical trials.

In a report from the Swedish Adult Acute Leukemia Registry by Lehmann et al. [20], patients aged 60 or more accounted for 38% of the entire group; their ED rate was 50% and 1-year and 5-year survival rates were 37% and 24%, respectively. In a population-based US study, Chen et al. [22] identified 449 patients (32%) aged 60 or more, with their 1-year and 5-year survival rates being 38% and 24%, respectively.

Different data were found by multicenter studies. In the cited studies [25-32], patients older than 60 years and those older than 70 years accounted for 6-26% and 3-9%, respectively. In these studies, elderly patients' treatment outcomes are slightly worse when compared with younger patients, with lower CR (82-90%) and higher ED (11-18%) rates. Long-term survival is observed in more than a half of elderly patients. The different outcomes are explained by selection of patients included in clinical trials, namely exclusion of mostly elderly patients unable to receive experimental chemotherapy due to comorbidities.

The presented results correspond with those obtained from clinical trials with patient selection rather than unselected population-based registers. The discrepancy may be due to the relatively small size of the group presented that cannot be statistically compared with data published in studies of large patient groups from multiple centers. Another possible explanation is that this rare condition is underdiagnosed. It cannot be ruled out that a certain proportion of individuals with the disease, in particular elderly patients, are not correctly diagnosed and referred to intensive hematology care centers. It is rather unlikely that over the last 20 years, there has been just a single case of fatal intracerebral hemorrhage in
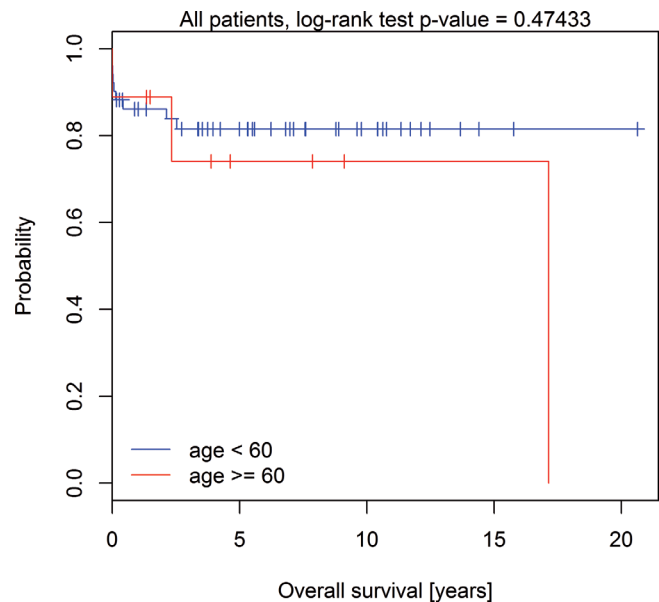

Figure 1. Kaplan-Meier curves for overall survival. OS as stratified by age.

an elderly APL patient in a catchment area with a population of approximately 1 million people.

On the other side, the reported results are very encouraging, showing the future direction of treatment for acute leukemia in elderly patients, the outcomes of which are globally still unsatisfactory.

Treatment of elderly patients with acute promyelocytic leukemia, if administered by an experienced team, may be very successful and its outcomes may be comparable with those achieved in younger age groups. Our experience shows that, unlike in the other forms of AML, a curative approach should always be attempted regardless of age, even in patients with significant comorbidities.

Table 3. Patients – basic characteristics

Gender	Age	Year of dg	Risk (Sanz)	HCT-CI	Therapy	Remission	Cause of death	Survival from diagnosis (years)
male	64	1994	intermediate	4	7+3/ATRA[1]	yes	myocardial infarction	17.1(+)
male	61	1999	low	3	GIMEMA	yes	peripheral T-NHL	2.3(+)
male	66	2000	high	4	-	no	CNS bleeding	3 days
female	69	2004	low	0	GIMEMA	yes	-	9.7
male	73	2005	intermediate	4	GIMEMA	yes	-	8.2
female	60	2008	low	3	PETHEMA	yes	-	5.5
male	70	2009	intermediate	0	PETHEMA[2]	yes	-	4.4
male	73	2012	low	8	individual[1]	yes	-	1.6
male	68	2012	intermediate	0	PETHEMA	yes	-	1.5

[1] see the text for details

[2] reduction – see the text

(+) dead patients

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