# Role of low dose cytarabine in elderly patients with acute myeloid leukemia: An experience

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## Abstract

**Purpose:** To highlight the acceptable results seen after use of low dose cytarabine in elderly patients of acute myeloid leukemia (AML) with comorbidities. **Materials and Methods:** This was a prospective study carried on 30 newly diagnosed patients of AML over 60 years of age who were unfit for standard treatment regimens. We did not use azacytidine and decitabine in our patients because these therapeutic modalities being extremely costly and our patient affordability being poor. After taking patient consent and institutional ethical clearance these patients were treated with 20 mg/m$^2$ cytarabine subcutaneously in two divided doses 12 h apart for 4 days every week for 4 weeks which constituted a cycle before disease, re-assessment was done. A repeat cycle was administered where ever needed and after attainment of remission, we continued low dose cytarabine for 2 days/week as maintenance after complete or partial response was documented. **Results:** In our study, we found that around 20% of patients achieved complete remission and 30% partial remission. The remission rates were definitely influenced by counts at presentation, performance at presentation, comorbidities, underlying myelodysplastic syndrome and baseline cytogenetics. **Conclusion:** Low dose cytarabine is effective treatment option for elderly patients with AML when standard treatment options are not warranted.


**Key words**: Comorbidity, elderly acute myeloid leukemia, low dose cytarabine

## Introduction

Acute myeloid leukemia (AML) was considered incurable and essentially fatal till 1959 Roberts, and Charles Dekker at the University of California, Berkeley, US.[1] Subsequent to this the advent of anthracyclines and its use in 3 + 7 chemotherapy [2,3] and allogeneic stem cell transplantation the cure rates have improved to nearly 65%[4].

The treatment and outcome of AML depends upon the age of the patient[5], performance status (PS)[6], comorbidities associated, underlying myelodysplastic syndrome (MDS), counts at presentation[7] and baseline cytogenetics.

The conventional chemotherapeutic regimen remains dangerous in elderly patients with associated comorbidities[8]. The reason for poor outcome in elderly is secondary to compromised organ function and comorbidities associated.

There have been many studies in the past which have demonstrated the efficacy of low dose cytarabine in AML in elderly[8]. Cytarabine has been shown to cause differentiation of leukemic cells into normal cells[9]. The mechanism of action of cytarabine at that time was poorly understood but with advances in molecular biology and pharmacology the mechanisms of this differentiation was discovered.

Cytarabine arabinoside is a pyrimidine analogue which acts by false incorporation into DNA causing reiteration of DNA segments, it also inhibits glycoprotein and glycolipid synthesis, alters membrane structure and antigenicity thus making more prone to natural immune mechanisms. Cytarabine induces ceramide synthesis, transcriptional factors like jun-fos and jun-jun and thus helps apoptosis [10,11,12,13]. So to summarize cytarabine acts at multiple levels, and this property of cytarabine makes it essential part of all AML treatment regimens what so ever its dosage may be.

The overall survival as described in the literature for conventional dose cytarabine is 38.7% when compared to 42.5% in the high dose cytarabine group. Complete remission (CR) rates of 72% versus 78.7% were observed with conventional dose and high dose respectively[14]. The cumulative incidence of relapse was significantly decreased in patients assigned to receive three to four cycles of high-dose cytarabine compared with patients assigned to one course (*P* - 0.03; 5 years CIR: 43% vs. 70%, respectively)[15].

## Materials and Methods

This was prospective study carried out on 30 newly diagnose AML patients over age of 60 years. A detailed history, general physical examination and baseline investigations were done. At first contact presenting count, blast percentage in blood, bone marrow morphology and immunocytochemistry were obtained. The marrow diagnosis was classified as per French–American–British classification and diagnosis was further confirmed by flow cytometry. In all patients, a baseline cytogenetics and FLT3 and NPM gene status was also obtained.

All patients were started on antifungal and antiviral prophylaxis after taking appropriate investigations. The patients whose performance score was ≥2 were enrolled in this study.

All patients received blood and blood product supportive care where ever needed in addition to treatment for tumor lysis syndrome.

We included newly diagnosed AML aged 60–70 with PS ≥2 in our study AML-M3, AML secondary to MDS, AML therapy related and AML with FLT3 and NPM positivity were excluded from the study. The endpoints for our study were patient's death, loss of follow-up, evidence of disease progression (medullary or extramedullary) or appearance of a new cytogenetic abnormality.

The drug cost was extremely low (approxmatiely 500–1000 INR in total).

After brief initial stabilization these patients were started on low dose cytarabine 20 mg/m$^2$ in two divided doses 12 h apart subcutaneously by a hypodermic needle 4 days every week for 4 weeks. After completion of one cycle bone marrow examination was done to look for remission status and as per need (partial remission [PR]) a second cycle was started. At end of the second cycle again an assessment for remission was done and in case of CR or PR patients were started on 2 days/week maintenance treatment, which was continued till the end point of study reached. After morphological remission

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was seen minimal residual disease remaining after initial chemotherapy was measured by flow cytometric detection of aberrant immunophenotypes and cytogenetic abnormalities were detected using reverse transcription polymerase chain reaction and fluorescence *in situ* hybridization techniques.

Remission criterion was followed as per guide lines given by Cheeson *et al*[16].

### Patient characteristics and results

Following tables depict patient characteristics and remission status. Table 1 shows baseline characteristics of all the patients. Table 2 shows remission status of all the patients and Table 3 depicts remission status relationship to baseline cytogenetics. In our study, we found that CR was attained in 20% of patients and PR in 30% of patients. The CR rate was highest that is, 33.33% with favorable cytogenetic groups of t (8:21) and inv (16). CR status was least Ithat is, 0% with complex cytogenetics (five or more abnormalities)[14].

Similarly, PR was also highest that is, 66.665 with a favorable cytogenetic group as mentioned above and least that is, 16.66% with a complex cytogenetic group.

Table 4 depicts survival data and shows longest survival duration of 24 months and average survival of 18 months. Table 5 shows comparison between various studies and our study.

**Table 1: Clinical characteristics at diagnosis**

| Characteristic | Value/status (%) |
|---|---|
| Age (range) | 60-70 years |
| Mean age | 66 years |
| Male/female ratio | 1.5 |
| Performance status | |
| 1 | 12 (40) |
| 2 | 18 (60) |
| WBC count (median) | 83.1 thousand |
| Blast percentage in BM (median) | 61 |
| Baseline median Hb (g/dl) | 7.3 g/dl |
| Baseline median platelets | 32,000 |
| Cytogenetics | |
| Normal | 18 (60) |
| t (8:21) | 3 (10) |
| Inv (16) | 3 (10) |
| Complex | 6 (20) |
| NPM-1 | Nil |
| FLT3 | Nil |
| Underlying MDS | Nil |
| Treatment related | Nil |
| FAB class | |
| M1 | 10 (33.3) |
| M2 | 18 (60) |
| M4 | 2 (7.7) |
| CNS/extramedullary disease | Nil |

WBC=White blood cell, BM=Bone marrow, MDS=Myelodysplastic syndrome, CNS=Central nervous system, FAB=French-American-British

**Table 2: Remission status of patients**

| | |
|---|---|
| Morphological CR | 2 (6.66%) |
| Cytogenetic CR | 4 (13.34%) |
| Molecular CR | 0 (0%) |
| CR (total) | 6 (20%) |
| PR | 9 (30%) |
| No response/worsening | 12 (50%) |

CR=Complete remission, PR=Partial remission

**Table 3: Remission status versus cytogenetics**

| Cytogenetic | CR (%) | PR (%) | NR/progression (%) | Total (%) |
|---|---|---|---|---|
| Normal | 4/18 (22.22) | 4/18 (22.22) | 10/55.55) | 18/30 (60) |
| t (8:21) | 1/3 (33.33) | 2/3 (66.66) | 0/3 (0.00) | 3/30 (10) |
| Inv (16) | 1/3 (33.33) | 2/3 (66.66) | 0/3 (0.00) | 3/30 (10) |
| Complex | 0/6 (0.00) | 1/6 (16.66) | 5/6 (83.33) | 6/30 (20) |
| Total remission | 6/30 (20) | 9/30 (30) | 15/30 (50) | 30/30 (100) |

CR=Complete remission, PR=Partial remission

## Discussion

In past low dose cytarabine has been used for treatment of acute nonlymphocytic leukemia, acute promyelocytic leukemia (APML) and MDS with acceptable results and acceptable toxicity profile. Treatment of AML in elderly has always been a challenge both in developed and developing world. Since we are presenting our data from a developing nation where finances, availability of newer treatment options and supportive care is always a concern treatment of elderly patients with poor performance with low dose cytarabine as already described in the literature is a good option.

We here present a protocol using low dose ara-C which produced an acceptable CR rate following two course of this regimen. High dose ara-C in induction therapy of AML has, in younger patients, resulted in improved response duration and long-term survival at the cost of an increased early death rate and subsequently no improvement in the CR rate. In contrast, our study provided a low early death rate and high CR rate. We used ara-C at a dose that was sufficient to saturate ara-CTP-levels in leukemic cells Baccarani *et al*. 1979 without excessive nonhematopoietic toxicity[17]. Aggressive chemotherapy has been used in a guarded manner in majority of centers however the Swedish Acute Leukemia Registry covers 98% of all patients with AML (non-APML) diagnosed in 1997–2005 ($n$ = 2767), with a median follow-up of 5 years, and reports eligibility for intensive therapy, PS, CR rates, and survival. Outcomes were strongly age and PS dependent. Early death rates were always lower with intensive therapy than with palliation only in their study. Long-term survivors were found among elderly given

**Table 4: Survival data**

| Characteristics | Result |
|---|---|
| Mean duration survival | 18 months |
| Longest survival | 24 months |
| Minimum survival | 3 months |
| Average inductions needed | 1.3 |
| Average improvement score | 1.4 |

**Table 5: Data comparison with other studies**

| Study | Baccarani and Tura | Moloney and Rosenthal | Weh *et al.* | Our study |
|---|---|---|---|---|
| No of patients | 21 | 48 | 16 | 30 |
| AML | 16 | 48 | 12 | 30 |
| MDS | 5 | - | - | - |
| Dosage | 10 mg/m$^2$ 12 hourly for 21 days | 10 mg/m$^2$ 12 hourly for 15 days | 10 mg/m$^2$ 12 hourly for 14-28 days | 20 mg/m$^2$ 4 days/week 4 weeks |
| CR % | 57 | 50 | 56 | 20 |
| CR+PR % | 71 | 64.5 | 74 | 50 |

CR=Complete remission, PR=Partial remission, AML=Acute myeloid leukemia, MDS=Myelodysplastic syndrome

intensive treatment despite poor initial PS. Total survival of elderly AML patients was better in the geographic regions where most of them were given standard intensive therapy. This analysis provides unique real world data from a large, complete, and unselected AML population, both treated and untreated, and gives background to treatment decisions for the elderly.

The overall survival data with the use of cytarabine in conventional and high dose regimen is approximately 40% with remission rates of 70–80% and relapse-free 5 years survival of 40-70%[15].

Standard intensive treatment improves early death rates and long-term survival compared with palliation. Most AML patients up to 80 years of age should be considered fit for intensive therapy, and new therapies must be compared with standard induction[12]. However, it needs a real strong support system, financial liberty and local experience in the treatment of elderly patients. Our study does not disagree with this work but just wants to highlight our observation with low dose cytarabine.

Many recent studies approve the use of hypomethylating agents (azacytidine and decitabine) for the treatment of AML in elderly patients with acceptable results and less toxicity profile and better patient tolerability.[13]

There have been various studies in the past which have shown the role of cytarabine in the treatment of AML. Baccarani and Tura[17], Moloney and Rosenthal[18], Housset *et al.*[19] introduced low dose cytarabine in the treatment of AML and MDS and observed CR and PRs. We carried this study with the intention to highlight our experience. In this study, we found that 20% of patients went into CR and 30% into PR. Castaigne *et al.*[8] in 1985 showed remission rates of 33%, which were slightly higher than our results possibly because of the higher number of patients and in addition no data on baseline cytogenetics is available in their study. Burnett *et al*. showed 18% remission rates with low dose cytarabine when compared to hydroxyurea with remission of only 1%.[22] In a study carried by Robles *et al*.[20] wherein he compared role of low dose cytarabine maintenance postcompletion of chemotherapy with observation only and found that the CR duration for low dose cytarabine (median: 12 months, 20% at 3 years) was significantly better ($P$ = 0.006) than for observation (median: 7 months, 7% at 3 years). The remission results varied with the type of cytogenetics, highest with t(8:21) and inv(16), intermediate with normal karyotype and least with complex karyotype. Similar results were seen by Weh *et al*.[21] The longest duration of survival in our study was 24 months, the average duration of 18 months and least duration of 3 months. Near similar results were seen in the study carried by Weh *et al*.[21] Roxane Nelson has considered cytogenetics as the strongest prognostic factor in his study in the treatment of AML with cytosine.[23]

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