

# Management of acute myeloid leukemia (AML) in elderly and resource constrained setting

## Abstract

Currently, only about 20% of Indian AML patients can afford the standard therapy of 7+3 followed by HIDAC. The stem cell transplant option is financially accessible to an even a smaller subset. There is a huge unmet need for an affordable treatment option for the vast majority of the population. We believe that our innovative approach of using lenalidomide with cytosine is a viable option for treating a vast majority of patients with elderly AML and relapsed AML who are financially challenged, and brings hope to this neglected demographic. Our elderly population is ever increasing due to increasing life expectancy, with resultant increase in elderly AML patients.

**Keywords:** lenalidomide, HIDAC, LDH, LFS, myeloblasts, acute myeloid leukemia

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## Case reports

### Case 1

A 65 year old apparently healthy male, presented with fever. His CBC showed pancytopenia with a Hemoglobin of 7.8gm/dl, WBC count of 2300/cmm and platelet count of 67,000/cmm. His peripheral blood smear showed 8 to 10% mononuclear cells—? Blasts. His LDH was mildly raised (678mg %). A bone marrow procedure was performed with the aspirate demonstrating 50–55% blasts which were MPO positive by cytochemistry. Flow cytometry on his aspirate confirmed the diagnosis as Acute Myeloid Leukemia. His PCR AML prognostic panel showed at (8, 21) translocation. His 2D–ECHO showed a 45% ejection fraction.

**Standard management:** Daunorubicin–45mg/m<sup>2</sup> vs 90 mg/m<sup>2</sup> or Idarubicin with Cytosine is the standard protocol followed. In a retrospective French study of 147 patients who received at least one dose of induction chemotherapy, 60 showed at (8; 21). There was an 88% CR rate and a 10% 8week early death rate. With a median follow up of 48 months, the 5year probability of OS and leukemia–free survival (LFS) was 31% and 27%, respectively. On multivariate analysis, high WBC count, poor PS, and del (9q) had a negative impact, and trisomy 22 and intensive consolidation when compared with maintenance therapy had a positive impact. Despite a CR rate of 88%, median LFS was only 18 months.

**Practical management:** The options that may be considered are Decitabine or azacytidine with or without lenalidomide. Once remission is achieved, HIDAC (Cytosine 3gm/m<sup>2</sup>) or IDAC (1gm/m<sup>2</sup>) may be considered as the core binding factor AML are extremely sensitive to cytosine. Cerebellar toxicity is a problem in elderly AML while on cytosine.

### Case 2

A 70 year old elderly diabetic and hypertensive male presented with nasal bleeding. His Hemogram showed a low Hb of 9.8 gm/dl, low platelet count of 23,000/cmm and a markedly raised WBC count of 102000/cmm.

His LDH was markedly raised 2334mg/dl.

PS– 80–85 % myeloblasts (as demonstrated by MPO positivity and presence of Auer rods), Bone marrow aspirate– 85–90 % blasts, Cytogenetics – 9q deletion.

**Standard management:** The results of intensive therapy (viz. FLAG–Ida) in elderly patients with poor PS remain poor. Although CR rates of 40% to 80% can be achieved, in highly selected populations, long–term survival is poor. Even in patients with favorable cytogenetics who have 80% CR rates, relapse rates are high. As such, novel strategies are needed. Median survival varies from 6 to 10months.

**Practical management:** We use a lenalidomide 10mg/m<sup>2</sup> for 21 days per month with 5 days of cytosine 50–100 mg/m<sup>2</sup>.

## Discussion

Acute myeloid leukemia (AML) is a hematological malignancy more commonly seen with elderly patients. Patients with the condition, who are older than 60 years, are internationally labeled as having elderly AML. The disease has a markedly poor prognosis with a mean five year survival rate of 15%. In addition to age, other factors associated with poor prognosis are certain cytogenetic abnormalities, increased toxicity to cytotoxic drugs and higher incidence of MDR and associated comorbidities. Therefore multiple factors must be considered when treating elderly AML.

Although population based studies have demonstrated better survival for all age groups when treated with intensive regimens, the optimal induction and post remission regimes for elderly patients is still unclear. The following factors should be taken into consideration when treating these patients: Performance status (PS), LDH, WBC count at presentation, percentage of bone marrow blasts, expression MDR and karyotype.<sup>1–3</sup> The standard management of AML involves the use of a combination of anthracycline and cytosine (3+7) in tandem with or without other agents.

## Our experience

AML in elderly, relapsed, refractory or financially challenged patients poses a unique challenge. Due to limitations in standard treatment protocols we considered a unique approach of attacking the leukemic stem cells with a combination of lenalidomide and low dose cytosine. We postulate a possible mechanism that low dose cytosine induces differentiation and lenalidomide, with its wide spectrum of biological activity, cuts the vascular endothelial growth factor supply, leading to remission.

The use of lenalidomide – cytosine offers an outpatient treatment option for these patients. Furthermore, while conventional treatment

in India can cost up to \$20000 for a 5 month cycle and carries with it a significant risk, the lenalidomide– cytosine option costs about \$200 per cycle or about \$1000 for a 5 months treatment course.

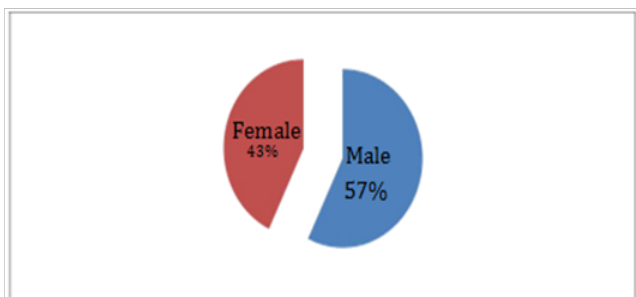
The outcomes in our retrospective analysis of 14 patients of AML

(Non AML M3) elderly AML (64%), relapsed refractory young AML– (36%) reveals survival of 10 months to few years are presented below.

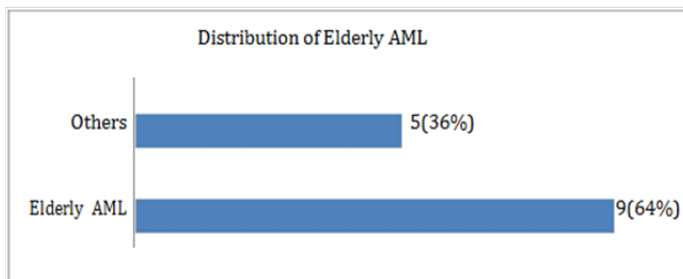
We have documented complete remission after a median of 60 days in 3 of our patients (Figure 1–6) (Table 1).

**Table 1** Summary of Patient data of lenalidomide and cytosine

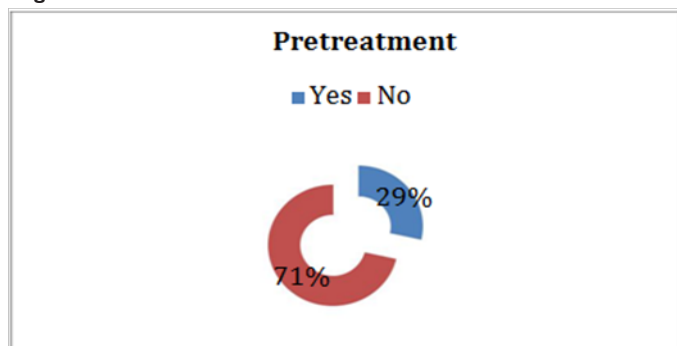
| Sr No | Age | Sex | Diagnosis           | PT | Treatment |     | OS Months | Living | HR | BM | Remarks<br>Thrombocytosis |
|-------|-----|-----|---------------------|----|-----------|-----|-----------|--------|----|----|---------------------------|
|       |     |     |                     |    | LEN       | Ara |           |        |    |    |                           |
| 1     | 64  | M   | Elderly AML         | N  | Y         | Y   | 52        | Yes    | Y  |    | Y                         |
| 2     | 72  | F   | Elderly AML         | N  | Y         | Y   | 18        | No     | Y  |    | Y                         |
| 3     | 68  | M   | Elderly AML         | Y  | Y         | Y   | 48        | Yes    | Y  |    | N                         |
| 4     | 52  | M   | Relapsed Refractory | N  | Y         | N   | 25        | No     | Y  |    | N                         |
| 5     | 79  | F   | Elderly AML         | N  | Y         | Y   | 11        | No     | Y  |    | Y                         |
| 6     | 66  | M   | Elderly AML         | Y  | Y         | Y   | 9         | No     | Y  |    | Y                         |
| 7     | 80  | F   | Elderly AML         | N  | Y         | Y   | 14        | Yes    | N  |    | Y                         |
| 8     | 68  | M   | Elderly AML         | Y  | Y         | Y   | 24        | Yes    | Y  | CR | Y                         |
| 9     | 69  | F   | Elderly AML         | N  | Y         | Y   | 12        | No     | Y  |    | Y                         |
| 10    | 71  | M   | Elderly AML         | N  | Y         | Y   | 18        | Yes    | Y  | CR | Y                         |
| 11    | 38  | F   | AML                 | N  | Y         | Y   | 18        | Yes    | Y  |    | Y                         |
| 12    | 58  | M   | AML                 | N  | Y         | Y   | 14        | Yes    | Y  |    | Y                         |
| 13    | 54  | M   | AML                 | N  | Y         | N   | 12        | Yes    | Y  | CR | Y                         |
| 14    | 42  | F   | AML                 | Y  | Y         | Y   | 1         | No     | N  |    | N                         |



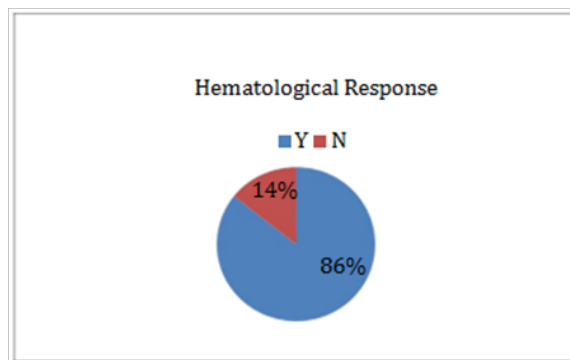
**Figure 1** Male to Female distribution.



**Figure 3** Percentage of Elderly AML.



**Figure 2** Percentage of patients with pre-treatment.



**Figure 4** Hematological Response was defined as transfusion independence (RBC and Platelets) and paucity of infectious complications.

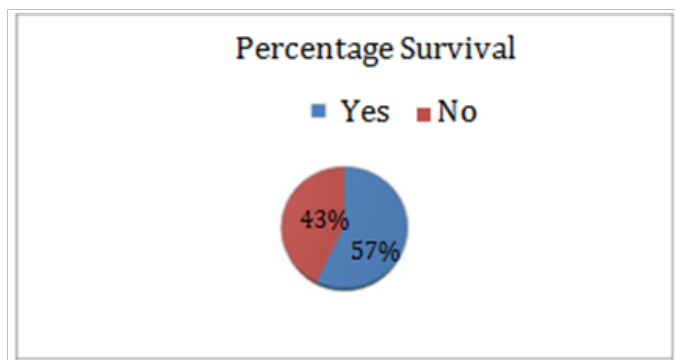


Figure 5 Percentage surviving patients.

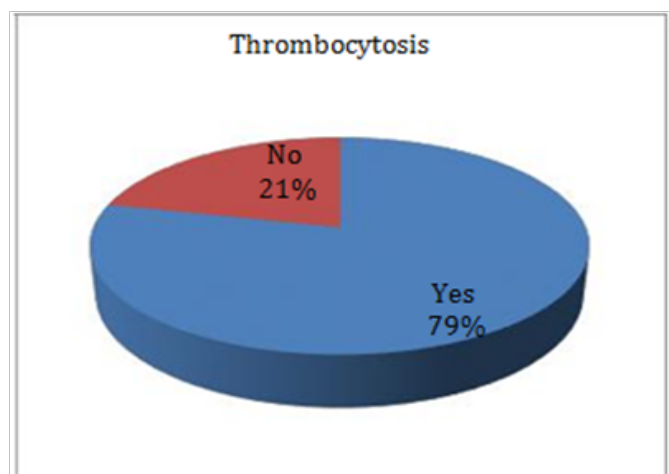


Figure 6 Percentage of patients developing thrombocytosis.

### Final consideration

The options for elderly AML are<sup>4</sup>

- I. Intensive chemotherapy needs good organ function, stay in hospital with intensive supportive care with few advantages.<sup>5</sup> It needs to be followed up by Consolidation, Long term survivors need allogenic transplant. The total cost in India would be \$40000 –\$75000 depending on the donor.
- II. Azacytidine vs decitabine needs hospital stay with risk of life threatening neutropenia with long term OS of 6 to 8months
- III. Best Supportive care OS of 4 to 6months

So we came up with the idea of combining Lenalidomide with Low dose Cytosine (LDAC). Lenalidomide has been used in scenario of 5q- MDS and AML.<sup>6</sup> But we have found that its effective in non-5q- scenario too.

### Few conclusions from our study are

- a) Lenalidomide–Cytosine is an option for the elderly AML patients who are hemodynamically stable
- b) Remission seems to take a longer time about 60 days.

- c) Low presenting count and lower rate of doubling time portends better rate of response, achievement of morphological CR and duration of response.
- d) The OS at 12 months was 60% for elderly AML in our small study.
- e) Thrombocytosis occurred in majority of patients and is early indicator of response. Anti-platelets need to be added for the same.
- f) The average cost of treatment was \$200 per month for 6 months.
- g) This treatment provided for better quality of life. Lesser stay in hospital, lesser antibiotic and blood product use.

### Moving forward we suggest

- i. The option of adding azacytidine or decitabine is being considered but with lenalidomide alone
- ii. Another approach that may be considered is the addition of an intermediate dose cytarabine after achieving remission
- iii. The effects of combining this with traditional options will need more clinical trials to elucidate.

### Conclusion

There is compelling evidence to pursue a milder, outpatient regimen in Elderly AML and AML who cannot afford conventional intensive treatment. Quality of life rather than just cure should be aim of treating elderly AML.

### Acknowledgements

None.

### Conflict of interest

Authors declare that there is no conflict of interest.

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