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Perspective

Treatment of elderly acute myeloblastic leukaemia with azacitidine after failure of decitabine

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Key words: acute myeloblastic leukaemia, azacitidine, decitabine

Summary

A 72-year-old man was seen with acute myeloblastic leukaemia (AML) after negligible response to four cycles of decitabine. Patient was treated with subcutaneous 5-azacitidine 75 mg/m^2 daily x 7 days/cycle. Patient achieved complete remission with incomplete recovery of blood counts (CRi) after 6 cycles and has been on maintenance cycles with the same schedule for another 8 months so far. There is very little data to support use of 5-azacitidine in elderly AML after failure of decitabine and hence this report.

Case report

A 72-year-old man was seen for AML. He had symptoms of weakness and episodic fever. There was easy bruising and one episode of epistaxis. Earlier, at another centre, he was diagnosed as AML 6 months earlier. He had presented with vague systemic symptoms, pancytopenia with marrow showing 30% blasts. During those 6 months, he had received 4 cycles of decitabine 20 mg/m^2 daily x 5 days per cycle as intravenous infusion therapy. Throughout this period, patient was off and on extremely sick due to anaemia and recurrent infections needing repeated hospitalizations and blood component support. Marrow repeated after 2 cycles had shown 28% blasts and the same after 4 cycles had shown 52% blasts. His subsequent treatment was abandoned and he was advised best supportive care.

At presentation to us, patient was sick, febrile with mild hepatosplenomegaly (1 cm each) and purpuric spots all over the body and oral cavity. His haemoglobin (Hb) level was 51 g/L, platelet count 26 x 10^9/L, WBC count 2.8 x 10^9/L with 18% blasts in peripheral blood and 78% blasts in the marrow. There were dysplastic changes in all 3 cell lines. Immunophenotyping confirmed AML with CD13, CD33, CD117, CD34, HLA-DR and cMPO positivity. Cytogenetic studies showed 7-monosomy. Molecular studies showed no evidence of nucleophosmin *(NPM1)* gene mutation or FMS-like tyrosine kinase-3 internal tandem duplication mutations *(FLT3/ITD)* mutation. Patient had performance status of two. He had no comorbidities.

He desired therapy with minimal toxicity over and above best supportive care. However, he had no interest in standard chemotherapy using 3+7 protocol or reduced intensity transplant. In view of this, he was started on subcutaneous (SC) azacitidine 75 mg/m^2 x 7 days every 28 days on outdoor basis. He was also on levofloxacin and voriconazole prophylaxis. The patient had local reactions at injection sites, episodic significant gastrointestinal disturbances and continuous requirement of blood products. However, by the end of third cycle, there was significant decrease in transfusion requirement and peripheral blood counts showed improvement. By the end of 6th cycle, he had a Hb level of 92 g/L, platelet count of 86 x 10^9/L (unsupported), WBC count of 6.4 x 10^9/L with absolute neutrophil count (ANC) of 4.9 x 10^9/L and no blasts in peripheral blood. Marrow examination showed good cellularity, minimal trilineage dysplasia with blasts < 1%. Cytogenetic studies showed persistence of 7-monosomy.

Patient was reluctant to continue further treatment. However, he was convinced and he continued the same treatment with almost no toxicity. By May 2015, he had completed total of 14 cycles

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and he was in complete remission (CR) with Hb level of 124 g/L, platelet count of 136 x 10^9/L, WBC count of 5.6 x 10^9/L with ANC of 2.9 x 10^9/L and no blasts in the peripheral blood. Bone marrow was not repeated.

Discussion

This is an interesting case where a number of lessons could be learnt.

The incidence of AML in patients over 70 years old is > 20 times greater than that observed in younger subjects. Elderly AML differ from young patients in various ways; high incidence of poor prognostic cytogenetic abnormalities, high incidence of therapy-related leukaemia, association with a prior haematological disease, often presence of multi-drug resistance gene expression and high incidence of comorbidities and poor tolerance to chemotherapy.

Overall, there is reluctance in treating elderly AML, especially in the developing world. Achievement of CR improves the quality of life and may also add to the duration of life. Hence, it makes sense to have a therapeutic plan with positive intentions even for such patients.

Although, there is no standard treatment regimen, elderly AML can be treated with one of the following options; standard induction therapy using 3+7 regime consisting of anthracyclin and cytosine arabinoside (Ara-C) with or without reduced intensity bone marrow transplantation, hypomethylating agents (HMA), low-dose cytosine arabinoside (LD-AraC), best supportive care (BSC) and clinical trial.

Standard induction therapy which is best for younger subjects may be the first choice even in elderly AML, however, there is early death of 15% in most of the studies. Development of hypomethylating agents (HMA) has brought out a new ray of hope in this group of AML patients.

Hypomethylating agents were discovered almost 50 years ago. Initially, they were used in high doses for treating AML. Results with 3+7 protocol were superior and hence HMA were almost forgotten. In early part of this century, the interest in HMA for treating myelodysplastic syndrome (MDS) was revived as their use in low dose worked as differentiating agents with good success and minimal toxicity. With accumulation of substantial data, 5-azacitidine received United States Food and Drug Administration (US-FDA) approval for treatment of MDS in 2004 and decitabine received the same in 2006.

Over last few years, HMA were considered as an attractive strategy for treating patients of AML who were otherwise considered unsuitable for 3+7 therapy. Azacitidine was compared with various conventional care regimens (CCR) which included LD-AraC, intensive chemotherapy or supportive care (phase 3 trial) in patients with intermediate-2 and high-risk MDS. Interestingly, 113 patients in this series had blasts between 20% and 29% and therefore, these were cases of AML with low blast counts. Complete remission rates were similar in the two arms (18% vs 16%)[1].

Subsequently, azacitidine vs CCR was studied in elderly AML with any blast count. Azacitidine showed improved median OS (10.4 months vs 6.5 months, p=0.08). This was statistically significant. A pre-planned sensitivity analysis censored for subsequent AML treatment showed a benefit in terms of median OS of 12.1 months vs 6.9 months for azacitidine[2]. Currently, azacitidine has licensed approval from European Medicines Agency (EMA) for AML with 20% - 30% blast cell count.

Decitabine 20 mg/m^2 daily for 5 days per cycle has also been studied against CCR in a phase 3 trial of 485 patients of AML above the age of 65 years. There was a higher response (CR + CRi 17.8% vs 7.8%) and better survival. This reached statistical significance (median OS 7.7 vs 5.0 months)[3]. Currently, decitabine has approval by EMA for patients of 65 years and above with AML who are not considered candidates for standard induction therapy.

Both azacitidine and decitabine have been approved by the US-FDA for AML with 20% to 30% of blasts. Studies have shown that Ten-Elevan-Translocation-2 *(TET2)* and DNA methyltransferase 3A *(DNMT3A)* mutated AMLs benefit from these epigenetic agents[4].

Decitabine has also been used in another more intensified dose schedule of 20 mg/m^2 daily for 10 days in 53 patients with median age of 74 years and the outcome was encouraging[5]. Complete remission rate was 47% and CRIi 17%.

Dombret *et al*.[6] have published the results of international phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. This is a study of 488 patients over the age of 65 years with newly diagnosed AML having over 30% marrow blasts. Median overall survival (OS) was longer with azacitidine vs CCR i.e. 10.4 months vs 6.5 months. Univariate analysis showed favourable trends for azacitidine compared with CCR across all subgroups. They concluded azacitidine as an important treatment option for this difficult to treat AML population.

Ramos F *et al.*[7] on behalf of European AML investigators have published their observations in using azacitidine as frontline therapy for unfit AML patients. This study includes newly diagnosed unfit patients of AML treated in France, Austria and Italy. European LeukaemiaNet response was achieved in 21.0% of 371 patients. This did not depend on bone marrow blast cell percentage. Median OS was 9.6 months and 40.6% of patients were alive at one year.

Lao Z *et al.*[8] concluded that treatment of azacitidine in elderly subjects with AML leads to fewer hospitalisation days and infective complications but similar survival compared with intensive chemotherapy.

Outcome of patients with AML who have failed treatment with HMA is poor. Median survival is 6 months. There is no established therapy available except allogeneic haematopoietic stem cell transplantation.

The choice between azacitidine and decitabine as the initial treatment of MDS or AML remains in dispute.

Our patient is unique from the angle that azacitidine worked after failure of decitabine. This goes to show that there are subjects where there may be no cross resistance between these two HMA. Recently, we have used azacitidine + lenalidomide after failure of decitabine with good success (unpublished observation). Future probably lies in rationally designed combination therapy in these otherwise difficult to treat patients.

Authorship

Contribution: This is the sole work of Dr. M.B. Agarwal.

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