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Original Research Article

A Comparative Study of Conventional Care Regimens and Azacitidine in the Patients Suffering from Higher-Risk Myelodysplastic Syndromes

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Abstract

In this study, azacitidine and conventional care treatments were compared for their average survival rates and their tolerance. The study was conducted on 87 patients having the age more than or equal to 75 years and suffering from the high-risk Myelodysplastic Syndrome.

Patients were selected randomly. Azacitidine was given to 38 patients of average age 75 Years, 75 mg/m^2/day subcutaneously x 7 days every 28 days. 49 patients were undergone conventional care treatments having an average age of 77 years. AZA significantly improved the Overall survival rate vs CCR (HR: 0.43 and 2-year Overall Survival rates were 56% vs 16%, respectively. In terms of tolerance, Azacitidine was observed to be better than the conventional care treatment. Comparatively, for Azacititnie and Conventional care treatment Grade, 3-4 anaemia was 13% and 4%, Neutropenia was 61% and 17% while thrombocytopenia was 50% and 30% respectively. After concluding the Tolerance limit and the effectiveness azacitidine can be the first-choice treatment in patients suffering from Myelodysplastic Syndrome.

Keywords: Azacitidine; Conventional Care Treatment, AML, RAEB, CMML.

Introduction

Myelodysplastic syndrome (MDS) is a diverse group of hematologic neoplasms that is often regarded as a clonal disease of hematopoietic stem cells. MDS causes bone marrow dysplasia and inefficient hematopoiesis. Some people with MDS may progress to acute myeloid leukaemia (AML) [1].

The ailment mainly affects elderly people (the average age at diagnosis is approximately 70 years), with 10 percent of occurrences occurring in people under the age of 50. In Europe, the annual incidence of

MDS and AML in adults is approximately 4 cases/100,000 and 5-8 cases/100,000, respectively, rising to 40-50 instances of MDS/100,000 and 15-25 cases of AML/100,000 in persons aged 70 years.[2] MDS and AML are now defined according to WHO criteria,[3] which encompass morphological characteristics, cytogenetics, molecular genetics, immunophenotype, and clinically relevant disease entities. Historically, MDS and AML were mostly classified using the French-American-British (FAB) criteria. The International Prognostic Scoring System (IPSS) criteria should also be used to identify the risk category for patients with MDS because a number of prognostic markers play a significant role in predicting clinical outcomes.[4] AML evolution and enhanced prognosis capabilities for survival were recently included in the IPSS criteria. Ageing, greater bone marrow blast (BMB) numbers, and multilineage dysplasia are prognostic variables linked to poor clinical outcomes.[5] The people who are suffering from MDS and come under the category of WHO- acute myeloid leukaemia (20-30% marrow blasts), as per the international multicenter randomized phase III AZA-001 trial, shows better overall survival rate with the azacitidine[6]. With a median age of 69 years, the participants in the AZA-001 trial tended to be older patients (range 38–88). A quarter of the randomized patients were 75 years of age or younger. This study was conducted in AZA-001 patients having the age more than 75 years. In this study toxicity and other outcomes were analyzed in the patients suffering from MDS or AML with 20–30% marrow blasts.

Methods

Patients: The eligible criteria for the patient who take part in the study were Age should be more than or equal to 18 years with higher-risk MDS (FAB: RAEB], [RAEB-t], or [CMML] with > 10 percent marrow blasts and a WBC count less than 13×109/Litre, and an IPSS risk of Intermediate-2 or High]). Candidates required to have an estimated life expectancy of under three months and an ECOG performance status of 0–2. Patients with therapy-related MDS, those who had previously taken azacitidine, and those who intended to get an allogeneic stem cell transplant were all disqualified. For this subgroup analysis, the effectiveness of all patients under 75 years old was assessed (intention-to-treat).

Study design: AZA-001 was a phase III, multinational, multicenter, randomised, controlled, parallel-group study, as previously reported. Before participating, all patients gave their signed, informed consent. Study recruiting and oversight were managed by site investigators and central pathology reviewers, and cytogenetic data were evaluated centrally in a consistent manner.

Patients selected randomly for the azacitidine will take it as 75 mg/m^2/day subcutaneously x 7 days every 28 days for not less than 6 cycles. While the patients selected randomly for the conventional care treatment will be treated as per the predefined regimen. There were basically three conventional care regimens like

- BSC (best supportive care): blood transfusions, antibiotics, and G-CSF for patients having few neutrophils.
- LDAC (low-dose are-C): 20 mg/m2/day subcutaneously x 14 days every 28 days for not less than 4 cycles
- intensive chemotherapy: includes induction with IV daunorubicin (45–60 mg/m^2/day), idarubicin (9–12 mg/m^2/day), or mitoxantrone (8–12 mg/m^2/day) for 3 days + 7 days ara-C 100-200 mg/m^2/day by continuous IV infusion

In this research BSC could be provided for all the candidates.

In the condition of hematologic toxicity, the dosing of azacitidine can be postponed to 1 or 2 weeks as per requirement, till the recovery from the hematologic toxicity.

As per protocol, there is ANC (absolute neutrophil count) was less than or equal to 1×109/Litre and /or platelet nadir was less than 50×109/Litre than dose can be postponed for the candidates whose baseline count of WBC is more than or equal to 3×109/Litre and ANC more than or equal to 1.5×109/Litre. Similarly, if WBC or ANC or platelet nadir decreased by more than or equal to 50% from baseline of WBC less than 3×109/Litre or ANC less than 1.5×109/Litre or platelets <75×109/Litre dose can be postponed.

Assessment of efficacy: Comparisons of the azacitidine and CCR treatment groups' efficacy were done. OS was the main efficacy objective. The IWG 2000 criteria for MDS [7] were used to measure the hematologic response (full [CR] and partial [PR] remissions) and hematologic improvement (HI), as well as the red blood cell (RBC) transfusion independence (TI) in patients who had RBC transfusion reliance at baseline. Patients required to have had at least 1 transfusion during the 56-day pre-baseline period before randomization in order to be classified as baseline RBC transfusion-dependent. A transfusion-free period of 56 consecutive days was considered as TI during therapy. The safety-evaluable group included all patients who received at least one dosage of study medication and had at least one safety evaluation. The results are shown for candidates who were preselected to receive BSC (n = 60) and then randomised to azacitidine or BSC, as well as patients who were preselected to receive LDAC (n = 24) and then randomised to azacitidine or LDAC. 3 Candidates were pre-selected for rigorous chemotherapy, with one receiving azacitidine and the other receiving CCR. Only one of the latter patients underwent extensive chemotherapy.

Hospitalization rates for adverse events in the azacitidine and CCR groups were assessed at 6 months and throughout the length of the trial. These rates were estimated as the number of hospitalisations per patient-year of medication exposure. This patient's adverse events are recorded descriptively rather than in data tables. The Common Toxicity Criteria, ver. 2, of the National Institute of Cancer was used to analyze adverse events. Hospitalization rates for adverse events in the azacitidine and CCR groups were evaluated at 6 months and throughout the duration of the trial. These rates were evaluated as the number of hospitalisations per patient-year of medication exposure.

Results

Patient disposition: In the AZA-001 study, the ITT population for this analysis consisted of 87 patients who were 75 years old at the study entrance. This subgroup's average age was 78 years old (with a range of 75 to 88), and the time from diagnosis (SD) was 1.0 to 1.7 years. Due to the initial randomization not being age-stratified, 38 patients were randomly assigned to receive azacitidine and 49 to receive CCR. The baseline features of the candidates in the azacitidine and CCR groups were comparable. At baseline, the majority of candidates required RBC transfusions and had an ECOG performance level of 0 to 1. 30 candidates (35%) satisfied the WHO-AML (20 to 30% blasts) criteria. Most of these older individuals were chosen to get BSC (60/87, 69%) prior to randomization. Candidates randomly assigned to the CCR arm (n = 49) were chosen for BSC in 33 (67%) cases, LDAC in 14 (29%) cases, and severe chemotherapy in just 2 (4%). Of the 38 candidates who were randomly assigned to get azacitidine and who subsequently received it, 27 (71%) had been

chosen for BSC, 10 (26%) for LDAC, and 1 (3%) for intense chemotherapy (Figure 1).

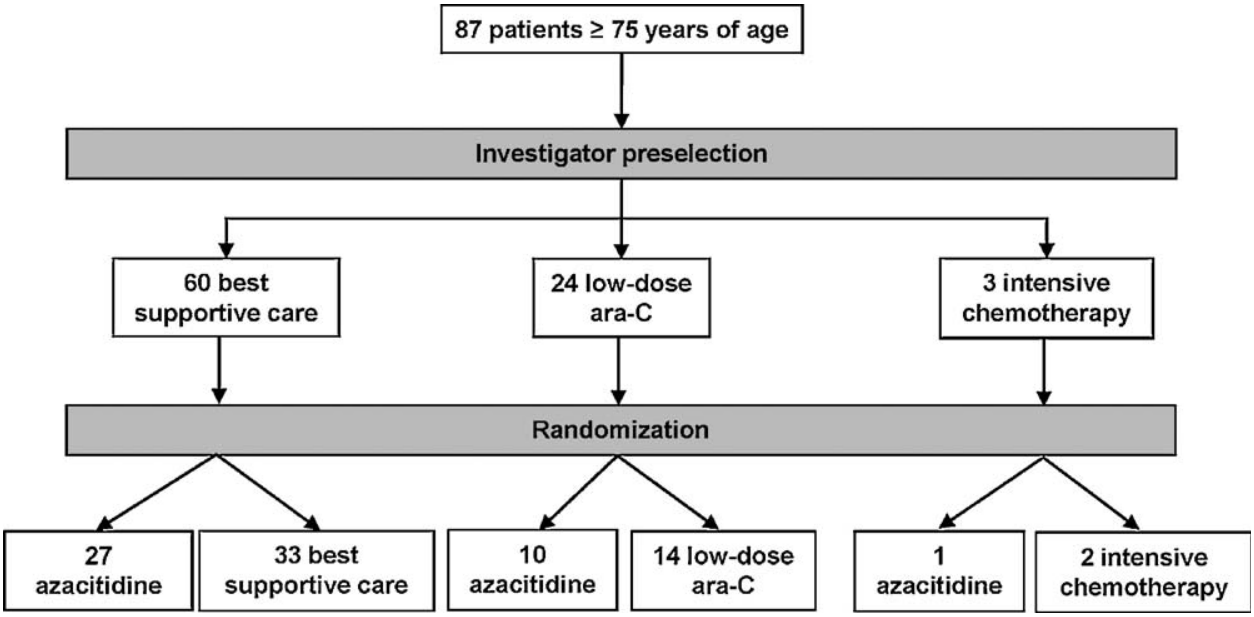

Figure 1: Patient disposition

Efficacy: The average amount of azacitidine cycles was 7.5 (between 1 and 23), whereas the average amount of LDAC cycles was 5.0. (Range 1 to 13). The average duration of an azacitidine treatment period was 28.0 days (21 to 106) and the average duration of an LDAC therapy period was 32.0 days (27 to 65). 51% of the 299 azacitidine periods that were given had a duration of less than 28, 26% had a duration of between 29 and 35 days, and 23% had a period of beyond 35 days. Of the 64 administered LDAC doses, 39% of cycle lengths were ≤28 days, 41% were between 29 and 35 days, and 20% were greater than 35 days.

In the azacitidine group, there were considerably more candidates who were still living at 2 years than in the CCR group: 55% vs. 15%, respectively (p 0.001). Compared to 22% of candidates in the combined CCR group, 43 percent (10/23) of azacitidine group candidates with baseline RBC transfusion reliance were able to attain RBC TI. 58% versus 39% (p = 0.09) of participants in the azacitidine and combined CCR groups, respectively, attained HI (major + minor) (Figure 2).

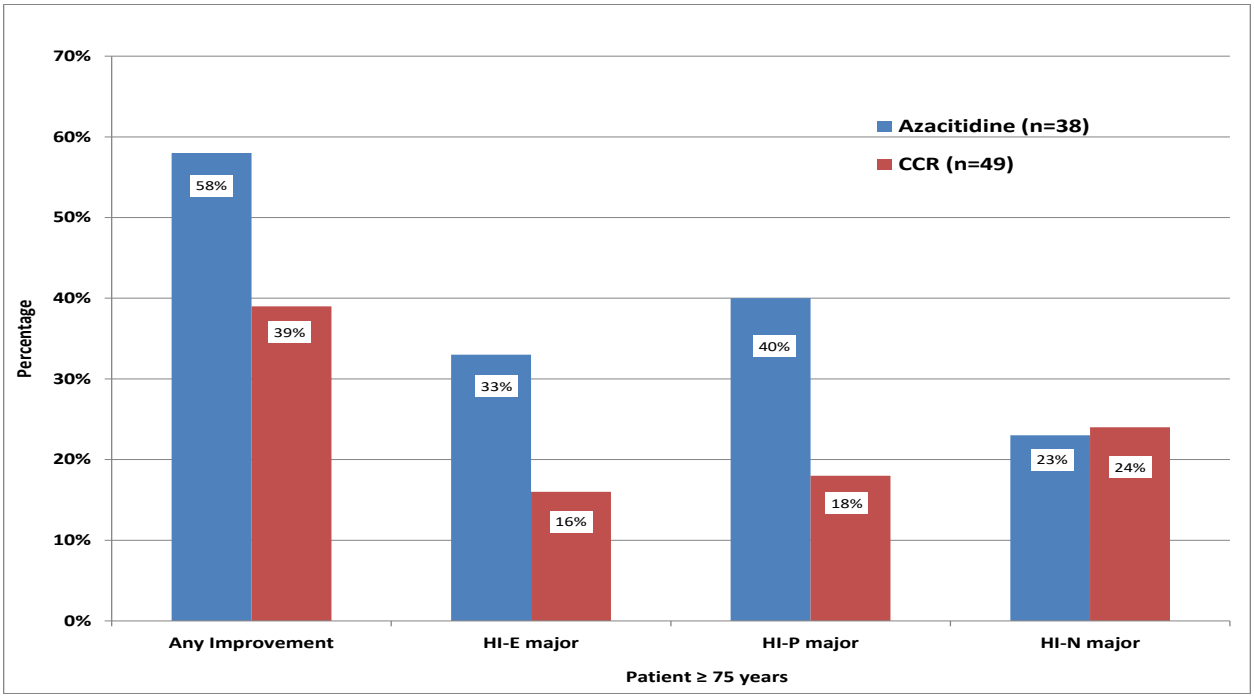

Figure 2: Hematologic improvement azacitidine vs CCR

Discussion

Azacitidine significantly increased OS in these older (75 years) individuals with higher-risk MDS, almost one-third of whom also met the criteria for WHO-defined AML (20 to 30 percent blasts), compared to the most frequently used conventional treatment regimens. In the study by Greenberg et al., untreated patients with MDS above the age of 70 who were given only BSC and were classified as IPSS Int-2 and High had median OS of about 1.2 years and 0.4 years, respectively.[8] Patients in our current research who got active azacitidine treatment and were on average older than those in the Greenberg study had much-improved survival rates: at 2 years, 55% of azacitidine-treated patients, with an average age of 78 years, were still alive. Only three (8%) of the azacitidine-treated participants in the current analysis passed away within the first 90 days of their randomization from illnesses that were judged to be connected to their study medication. In this senior population, there were not enough patients who had intense chemotherapy to evaluate its effects on OS.

Conclusion

The findings of this subanalysis add to the scant information that is currently known about the effectiveness of active treatment in elderly (>75 years) patients with higher-risk MDS or AML with 20–30% blasts. They show that azacitidine, which is normally well tolerated in these individuals with good performance status, can dramatically lengthen survival.

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