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Original Article

DECITABINE FOR MYELODYSPLASTIC SYNDROME AND ELDERLY ACUTE MYELOID LEUKEMIA- A TERTIARY CENTRE DATA FROM INDIA

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ABSTRACT

Objective: To assess the clinical profile of patients receiving Decitabine for myelodysplastic syndromes (MDS) and Acute myeloid leukemia (AML).

Methods: 14 patients had been initiated on Decitabine which included 11 MDS patients and 3 AML patients. Response was defined for MDS according to the International Working Group (IWG) 2006 criteria, whereas for AML according to IWG-AML 2003 criteria. Toxicities were graded according to the National Cancer Institute/Common Toxicity Criteria guidelines, version four.

Results: Out of the 14 patients overall response was achieved in 7 patients (50%) including 4 complete remission (29%), 1 partial remission (7%) and 2 stable diseases with hematological improvement (HI-N 1, HI-P 1 (14%). In case of MDS over all response was found in 6 patients (55%) including 3 patients with CR (27.5%), 1 PR (9%) and 2 stable diseases with HI (27%). Out of 14 patients 5 patients showed treatment failure (36%). One MDS patient showed disease progression and other one discontinued Decitabine. The most commonly occurred adverse effect noted was neutropenia which was observed in 13 patients (92.85%) and least commonly occurred were fatigue (13%) and fever (13%).

Conclusion Almost similar efficacy and safety profile were observed after comparing our data with ADOPT trial conducted by David P Steensma et al. The patients with MDS and AML had a lower median age at presentation compared with western data. We also noticed a worsening of pre-existing renal dysfunction observed in one patient after the second cycle of Decitabine which reversed upon stopping the drug.

Keywords: MDS, AML, Decitabine, IWG, Neutropenia.

INTRODUCTION

Myelodysplastic syndromes (MDS) is a heterogeneous group of clonal stem cell disorders, with hypercellular bone marrow, peripheral cytopenias, and dysplasia in both peripheral blood and bone marrow.[1] Acute Myeloid Leukemia (AML) is a form of cancer that affects the cells producing myeloid blood cells in the bone marrow. Myeloid cells are red blood cells, platelets and all white cells except lymphocytes. Almost all cases of AML affect those cells in the bone marrow which produces white blood cells. More rarely AML may affect other cells in the bone marrow which produce red blood cells or platelets. [2]

Decitabine is an "antimetabolite" and a "demethylating" agent was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of Myelodysplastic Syndromes (MDS) and Elderly Acute myeloid leukemia (AML). It is a Deoxycytidine analog, cell cycle specific with activity in the S-phase.[3] Western studies [4],[5] have already proven the safety and efficacy of Decitabine in the treatment of MDS and AML patients. To the best of our knowledge, this is the first Indian data focusing on safety and efficacy of Decitabine.

MATERIALS AND METHODS

Non-experimental (observational), both Retrospective and prospective follow up study was carried out on patients at the Medical Oncology and Haematology Department of Amrita Institute of Medical Sciences(AIMS) Kochi, from December 2012 to June 2013. The study was carried out after getting approval from the Research and Ethics Committee. Patient's data of all the MDS and AML patients of medical oncology department, taking decitabine are collected and those satisfying the inclusion and exclusion criteria were selected for the study.

Classification

MDS was categorized according to the World Health Organization (WHO) and IPSS classification and AML as per the criteria of FAB/WHO.[6]

Treatment

Approved dose of Decitabine is 20 mg/m^2 administered as a 1-hour IV infusion once daily on 5 consecutive days and cycle repeated every 4 weeks. Cycle was repeated until a suitable response was achieved. Decitabine is stable in room temperature up to 8 hours when diluted in 100 ml normal saline. Individual dose was calculated based on the patients BSA. All patients received the same Decitabine total dose per course, 100 mg/m^2 in 1 cycle.

Assessment of efficacy

Response was evaluated after Decitabine treatment by blood count, bone marrow aspirate, and cytogenetic studies. Response was defined for MDS as an achievement of complete response (CR), partial response (PR), marrow CR(mCR) or hematologic improvement (HI) according to the International Working Group (IWG) 2006 criteria [7],for AML as achievement of CR, PR, or CRi (ie, CR with incomplete recovery of cytopenias) according to IWG-AML 2003 criteria.[8]

Assessment of safety

Toxicities were graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Grade refers to the severity of the adverse event. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe, Grade 4 Life-threatening consequences and Grade 5 Death related to AE.

RESULT

Pretreatment characteristics of the patient population

The study population consisted 9 men and 5 women, with median age for patients suffering from MDS and AML was found to be 57 and 63 respectively. As per the criteria of the International prognostic scoring system (IPSS) 9 patients come within intermediate risk 1 and 2 patients within intermediate risk 2 (Table 1). From this classification, it was found that more number of patients are

included in intermediate risk 1. According to the WHO classification of MDS it was found that 4 patients were in RAEB 1, 4 patients in RAEB 2 and 3 patients in RCMD. According to the FAB classification of AML, 2 patients were included in M1 and 1 patient in M2. Karyotype of patients with MDS and AML, Data shows a majority of patients having good karyotype and two MDS patients with abnormal karyotype. Fig 1 illustrates the percentage of bone marrow blasts in patients before Decitabine therapy. From this data it was found that majority of MDS patients with <5% bone marrow blasts and AML patients with >20 % of bone marrow blasts.

Table 1: Pretreatment characteristics of the patient population

Demographic details	No of patients	Disease variables	No of patients
Age distribution (year)		**IPSS risk subgroup (MDS)**	
29-39	2	Intermediate-1	9
40-49	0	Intermediate-2	2
50-59	4	**FAB/WHO classification**	
60-69	4	MDS RAEB 1	4
70-79	4	MDS RAEB 2	4
Gender distribution		MDS RCMD	3
Male	9	AML M 1	1
Female	5	AML M 2	2

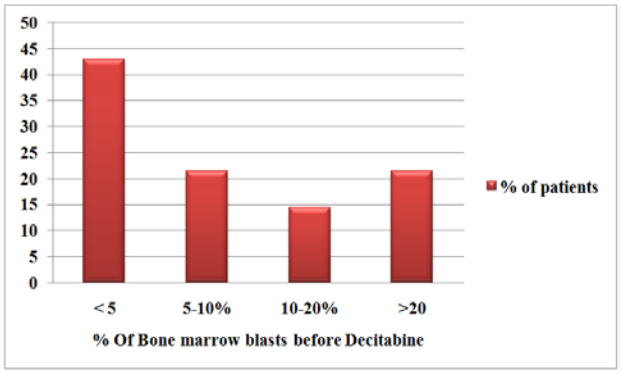

Fig. 1: Percentage of bone marrow blasts before treatment

Table 2: Responses to Decitabine chemotherapy in having MDS and AML

	Total (n=14)	AML (n=3)	MDS (n=11)
RESPONSES			
CR, n (%)	4(29)	1(33)	3(27.5)
PR, n (%)	1(7)	-	1(9)
Stable with HI, n (%) (HI-N 1,HI-P 1)	2(14)	-	2(27)
Disease Prorgression, n (%)	1(7)		1(9)
Treatment Failure, n (%)	5(36)	2(67)	3(27.5)
Treatment discontinued, n (%)	1(7)	-	1(9)
OVERALL RESPONSE RATE	**7(50)**		
CR n (%)		**1(33)**	
CR+PR+stable with HI, n (%)			**6(55)**

Assessment of efficacy

Response was defined for MDS according to the International Working Group (IWG) 2006 criteria18; for AML according to IWG-AML 2003 criteria. Table 2 Illustrates the responses achieved in 7 out of 14 patients, including 4 CR (29%), 1 PR (7%) and 2 stable diseases with hematologic improvement (14%; HI-N 1 and HI-P 1). Five of the 14 patients had Treatment Failure (36%) and one patient discontinued the treatment after 2nd cycle (7%). Also noticed was one patient with disease progression (7%) after 4th cycle of Decitabine. Over all response rate was found to be 50 %. Response rate in MDS patients was 55 % and AML patients with 33 %.

Assessment of safety

Fig 2 shows frequency distribution of various adverse reactions that occurred during Decitabine chemotherapy in MDS and AML patients. Most common adverse drug reaction found in patients treated with Decitabine was neutropenia which belongs to the grade 2, grade 3, grade 4 and grade 5 of adverse drug reaction categorization (Table 3). Grade 5 adverse drug reactions included sepsis. Fatigue, Fever and Pneumonia came under grade 2 and grade 3 categories. Nausea and vomiting were observed only in limited no. of patients and belongs to the Grade 1 and 2. We also noticed the worsening of pre-existing renal dysfunction (Figure 3) observed in one patient after the second cycle of Decitabine which reversed upon stopping the drug.

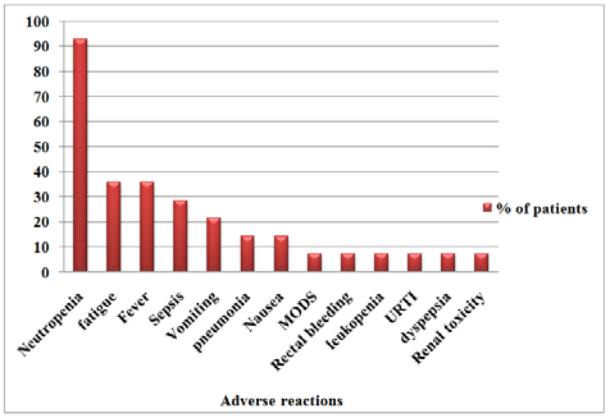

Fig. 2: Frequency distribution of adverse reactions

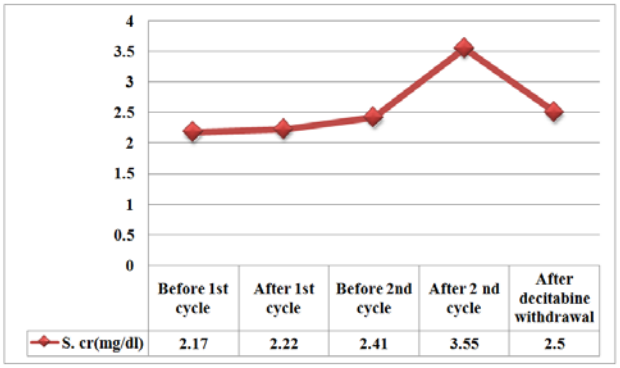

Fig. 3: Serum creating nine level of patient before and after treatment

Table 3: Grading of adverse effects of Decitabine in MDS and AML patients

Adverse effects	Grades	Total no. of patients
Neutropenia	Grade 2	4
	Grade 3	4
	Grade 4	2
	Grade 5	3
Fatigue	Grade 2	3
	Grade 3	2
Fever	Grade 2	3
	Grade 3	2
Sepsis	Grade 2	1
	Grade 5	3
Vomiting	Grade 1	3
Pneumonia	Grade 2	1
	Grade 3	1
Nausea	Grade 2	2
MODS	Grade 3	1
Rectal bleeding	Grade 2	1
Leukopenia	Grade 1	1
URTI	Grade 3	1
Dyspepsia	Grade 1	1
Renal toxicity	Grade 2	1

DISSCUSION

This study population consists of 9 men and 5 women and the median age of patients suffering from MDS and AML was found to be 57 and 63 respectively. The multicentre ADOPT trial conducted by David P Steensma et al,[4]found the median age for patients suffering from MDS was 72 and a multicentre phase 2 study conducted by Amanda F Cashen et al [9]found the median age of patients suffering from AML to be 74. The present study showed a lower median age when compared to other studies. The median number of Decitabine cycle was 4 (range 1-11) in the present study. Patients received a median of five cycles of Decitabine therapy (range, 1-17 cycles), and 38% of patients received eight or more cycles in ADOPT trial. In 2 previous Phase II Decitabine studies the median number of Decitabine cycles was similar (median of 4 cycles). Assessment of Decitabine response according to the modified IWG criteria: Total 14 patients were treated with Decitabine. In this, over all response was achieved in 7 patients (50%) including 4 complete remission(29%), 1 partial remission(7%) and 2 stable diseases with hematological improvement(HIN-1,HIP-1). In case of MDS over all response was found in 6 patients(55%) including 3 patients with CR(27.5%),1 PR(9%) and 2 stable diseases with HI(27%). In ADOPT trial, the ORR was 32% (17 complete responses [CR] plus 15 Marrow CRs [mCRs]), and the overall improvement rate was 51%, which included 18% HI. In this study response rate of AML patients were found to be33 %(1 CR). Out of 14 patients, 5 patients showed treatment failure (36%), including 3 in AML and 2 in MDS. One patient showed disease progression after Decitabine therapy. The median time to initial clinical response was after the second cycle (range 1-4) [57%] and median response for the duration of improvement was 4 months (range 3-11). In ADOPT trial 82% demonstrated responses by the end of cycle 2. Out of 14 patients, the most commonly occurred adverse reaction was neutropenia and was observed in 13 patients (92.85%). This data was supported by the study conducted by Kantarjian H et al.[29]In the ADOPT trial, cytopenia was the most commonly reported grade 3 adverse events at rates of 31% for neutropenia, 18% for thrombocytopenia, 14% for febrile neutropenia, and 12% for anemia. In this study, the least commonly observed adverse drug reactions were fatigue (35.71%) and fever (35.71%) and belongs to grade2 and grade 3. Severe neutropenia and sepsis were categorized under grade 5 toxicities as they were the reasons for mortality. Minimum number of patients showed nausea and vomiting with grade 1 and 2. ADOPT trial also reported nausea and vomiting with grade 1 and grade 2. Adverse drug reactions like fever, sepsis pneumonia, URTI accounted for prolonged hospital stay and patient care. There were no changes found in laboratory parameters like AST and ALT after the Decitabine chemotherapy as compared to the values prior to drug administration. Notably, febrile neutropenia occurred most commonly in the first cycle, particularly in 10% of patients. 32% of patients had delayed therapy mostly because of myelosuppression at a median of 8 days and 19% of administered cycles were associated with a hospitalization. Management of adverse effects, especially myelosuppression is essential to prevent early discontinuation of Decitabine therapy before achieving therapeutic benefit. Other clinically important factors that were observed in the study were Decitabine induced worsening of renal function in one patient and prolonged neutropenia (1-2 months) in another. However, no such cases were reported in any of the previously published studies. Even though our study was of short duration with small number of patients, these are relevant factors to be considered. So we propose further research about the above mentioned relevant factors. Almost similar efficacy and safety profile was observed after comparing this study and ADOPT trial.

CONCLUSION

Myelodysplastic syndromes (MDS) are clonal bone marrow malignancies characterized by peripheral cytopenias and dysplastic changes in the bone marrow with various clinical features and for this life threatening disease, the treatment options were scarce. Dectabine emerged as a new solution for MDS treatment. International studies were conducted and Decitabine proved to be effective in the treatment of both MDS and AML. This study was conducted to give more information and data regarding the clinical efficacy and safety of Decitabine in Indian population. These data will surely reinforce the effectiveness of Decitabine and will definitely help healthcare professionals to treat MDS which was difficult to treat once. One of the main highlights of this study was the Decitabine influence in the renaly impaired patients. Decitabine was found to increase the serum creatinine level of one patient and this data will help to conduct further studies about its influence in renal impaired patients. Important information observed in one patient was that Decitabine induced prolonged neutropenia. Inspite of it being a life threatening disease, we were able to evaluate the efficacy with the available patients. Out of the small sample size, most of the patients showed significant hematological improvement. The most remarkable improvement appeared to be in the platelets. Most of the patients showed good response even after the second cycle. It was interesting to observe the different responses like early response, late response and no response in patients. Compared to other chemotherapy, vomiting was very mildly induced by Decitabine and even reported events belong to grade1 only. Thus, this can be a very promising treatment available for MDS patients.

Abbreviations

MDS: Myelodysplastic syndromes

AML: Acute Myeloid Leukemia

WHO: World Health Organization

RA: Refractory anemia

RARS: Refractory anemia with ring sideroblasts

RAEB: Refractoryanemia with excess blasts

FAB: French-American-British

IPSS: International Prognostic Scoring System

CR: Complete remission

PR: Partial remission

HI: Hematologic improvement

HI- N: Hematologic improvement in neutrophils

HI -P: Hematologic improvement in platelets

FDA: Food and Drug Administration

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