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THE TREATMENT WITH HYPOMETHYLATING AGENTS IN MYELODYSPLASTIC SYNDROME AND ACUTE MYELOID LEUKEMIA

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Abstract. The hypomethylating agents such as azacitidine (AZA) and decitabine, have received FDA approval for the treatment of myelodysplastic syndrome (MDS) and chronic myelo- monocytic leukemia (CMML)[1]. The clinical studies demonstrated that treatment with hypomethilating agents (5-azacytidine and decitabine) in intermediate/high risk MDS resulted in complete responses in some cases. Also for patients with acute myeloid leukemia (AML) who do not qualify for aggressive chemotherapy and allogeneic medullary transplantation, treatment with hypomethilating agents leads to transfusional independence and increase in quality of life. We present the evolution under treatment with hypomethilating agents in 13 patients, diagnosed with intermediate/high risk MDS and AML in our Department between 2009-2014. There were 7 men and 6 women, with ages between 56-84 years, 6 of them diagnosed with intermediate 1 and 2 risk MDS, and 7 diagnosed with AML, unfit for chemotherapy. The selected schedules were: 5-Aza 75 mg/m2/d, for 7 days, repeated every 28 days and Decitabine 20mg/m2/d, for 5 days, repeated every 28 days. Results: All patients had a good tolerance to therapy, without significant adverse events. The overall response to 5-Aza was heterogeneous, with no considerable differences regarding blast percentage, with one complete response in the case with 12 monosomy. Unfortunately in 3 patients with AML treated with Decitabine, there was a delay in the time of treatment initiation due to administrative and financial issues, and they died due to disease progression. There were no side effects. The presented data indicate similar results to those in literature. The most important effect of treatment was increase in the quality of life by the reduction in the transfusional demand.
Key words: azacitidine, decitabine, MDS, AML

Introduction

Myelodysplastic syndromes are clonal diseases of hematopoietic stem cell, characterized by hypercellular marrow, dysplastic morphologic changes, ineffective hematopoiesis and evolution to acute leukemia. To date, allogeneic hematopoietic stem cell transplantation is the only therapeutic modality that can offer prolonged remission or even cure. However,,most patients are not candidates for anallogeneic transplant due to their age of presentation or a comorbidity. Moreover,disease relapse still remains an issue in these patients [1,2,3,4].

Therapeutic strategy in myelodysplastic syndromes depends on the risk group staging. The review of the prognostic models in literature highlights that prognostic in MDS patients relieson different risk models, some being disease related: French-American-British system (FAB), World Health Organization classification, International Prognostic Scoring System (IPSS), WHO Prognostic Scoring System (WPSS), MD Anderson Scoring System (MDACC), while others being patient and comorbidities related: MDS-specific Comorbidity Index (MDS-CI) [5,6,7,8]. In 2012, Peter L. Greenberg and collaborators published in Blood a material on The Revised International Scoring System (R-IPSS) that included MDS patients in five risk groups, based on cytogenetic changes [9,10].

For the MDS intermediate/high risk patients guidelines contain recommendations for therapy with hypomethylating agents[11]. In December 2014, at ASH, Professor Sekeres M has reviewed existing therapeutic approaches and clinical trials in MDS [12] and Poster session contained important papers on the role of treatment with hypomethylating agents in MDS, including "SIRPB1 is a strong predictor biomarker of response to 5-Aza therapy in MDS and AML patients"

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(V.Guadagnuolo, Bologna). The hypomethylating agents, such as azacitidine and decitabine, have received FDA approval for the treatment of myelodysplastic syndrome (MDS) and chronic myelo- monocytic leukemia (CMML). The clinical studies demonstrated that treatment with hypomethilating agents (5-azacytidine and decitabine) in intermediate/high risk MDS resulted in complete responses in some cases. Also for patients with acute myeloid leukemia (AML) who do not qualify for aggressive chemotherapy and allogeneic medullary transplantation, treatment with hypomethilating agents leads to transfusional independence and increase in the quality of life.

We present our experience with azacitidine and decitabine in the treatment of intermediate 1 and 2 risk MDS and AML.

Material and method

We assessed characteristics of 13 patients, diagnosed with intermediate 1 and 2 risk for MDS and AML, in our Department between 2009 – 2014, who were treated with azacitidine or decitabine. All patients met WHO criteria for diagnosis. WE used the IPSS score sistem for inclusion of MDS patients in different risk groups.

There were 7 men and 6 women, with ages between 56-84 years, 6 of them diagnosed with intermediate 1 and 2 risk MDS, and 7 diagnosed with AML, unfit to chemotherapy. 10 patients (6 patients with MDS and 4 patients with AML) received treatment with 5-azacytidine and 3 patients, one man with AML post MDS and 2 women with AML de novo, received Decitabine.

Cytogenetic exam was performed in all cases and a abnormal karyotype was obtained in 3 cases: one female patient with AML post MDS with del (5) (q32;qter), one patient with MDS, with a complex karyotype, including del (5)(q32;qter) and one patient with MDS and 12 monosomy.

The selected schedules were: 5-Aza 75 mg/m2/d, for 7 days, repeated every 28 days and Decitabine 20 mg/m2/d, for 5 days, repeated every 28 days.

An intravenous 5-HT3 antagonist was given as an anti emetic before each drug administration. Erythropoiesis-stimulating agents(ESA) administration and growth factors were not allowed for the patients with MDS high/intermediate risk and AML. Transfusion of blood products was done according to the guidelines and clinical evolution. Antibiotic prophylaxis was used when deemed necessary by the treating physician.

Response was assessed by modified IWG criteria [13]. Complete remission (CR) was defined as BM blast count </=5%, with normal maturation of all cell lines for at least 4 weeks and the presence of a PB neutrophil count of >/= 1.0 X 109/L, platelets >/= 100 X 109/L, hemoglobin >/= 11 g/dL, and no PB blasts were required. Partial response (PR) required that all criteria for CR be met, except BM blasts decreased by >/= 50% over pre treatment but still >5%. Stable disease (SD) was defined as failure to achieve at least PR and no evidence of progression for >8 weeks. Patients not achieving at least PR were further assessed for hematological improvement (HI) by using the IWG criteria for MDS. Hematologic improvement (HI) was reported as follows: erythroid response required a hemoglobin increase by at least 1.5 g/dL or reduction in transfusion requirements. If baseline platelets were <20 X 109/L, a response required an increase by at least 100% and to more than 20 X 109/L. If baseline platelets were more than 20 X 109/L, a response required an absolute increase of at least 30 X 109/L. Neutrophil response referred to a granulocyte increase by at least 100% over baseline and by an absolute increase of at least 0.5 X 109/L. Progressive disease (PD) was defined as a >/= 50% increase in BM blast cells or at least 50% decrement from maximum response in granulocytes and platelets, reduction in hemoglobin by >/= 2 g/dl and transfusion dependence. HI had to be sustained for at least 8 weeks. Bone marrow aspirates and biopsies were reviewed by pathologists at our institution. Overall response rate (ORR) was defined as the sum of CR, PR, and HI[1].

Survival was measured from the start of therapy.

Data were summarized using median, range, and percentage.

Results

The male to female ratio was 1,6:1. The median age of our cohort was 70 years (range, 56-84 years). Median age for males was 70 years (range, 56-84 years). Median age for females was 71,5 years (range, 64-79 years). Overall, 6 of them (46,2%) diagnosed with intermediate1 and 2 risk MDS, and 7patients (53,8%) diagnosed with AML, according to WHO classification. 1 (7,7%) patient had refractory anemia with excess blasts 1(RAEB 1), 4 (30,8%) had RAEB 2, 1(7,7%) patient had CMML 1, 1 (7,7%) had AML 1, 2 (15,4%) had AML 4, 1 (7,7%) had AML 5b and 3 (23%) patients had secondary AML post MDS, according to WHO classification(Fig.1).

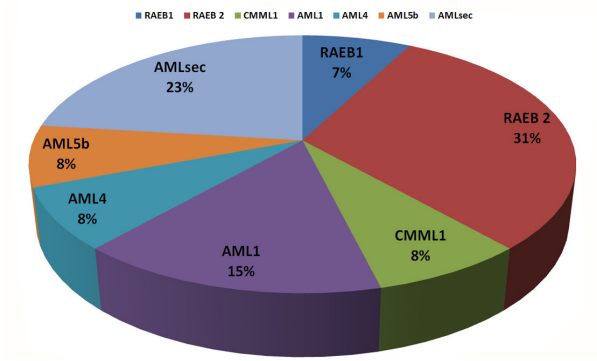

Fig.1.Diagnosis

Stratification by the International Prognostic Scoring System (IPSS) for MDS patients was as follows: intermediate-2 (4 from 6 patients with MDS), intermediate-1 (2 from 6 patients with MDS). All cases with AML unfit for standard induction therapy were considered high risk.

Cytogenetic exam was performed in all cases and an abnormal karyotype was obtained in 3 cases: one woman with AML post MDS with del (5) (q32;qter), one patient with MDS, with a complex karyotype, including del (5)

(q32;qter) and one patient with MDS and 12 monosomy.

Overall, 10 patients (6 patients with MDS and 4 patients with AML) received treatment with 5-azacytidine and 3 patients, one man with AML post MDS and 2 women with AML de novo, received Decitabine. The selected schedules were: 5-Aza 75 mg/m2/d, for 7 days, repeated every 28 days and Decitabine 20 mg/m2/d, for 5 days, repeated every 28 days.

Statistical analyses were performed only for the AZA-treated patients, because all three patients receiving Decitabine died due to disease progression genertaed by a delay in the treatment initiation, caused by to administrative and financial issues.

Pathology and responses were assessed internally at our institution. The median number of cycles of azacitidine given was 8,5 (range, 2 to 15 cycles). Overall response rate was 70% (7 of 10 patients). Response was stratified as follows: CR rate was 10% (1 of 10 patients), PR rate was 10% (1 of 10 patients), and HI rate was 50% (5 of 10 patients). Furthermore, 3 (30%) patients had progressive disease(PD) (Fig. 2).

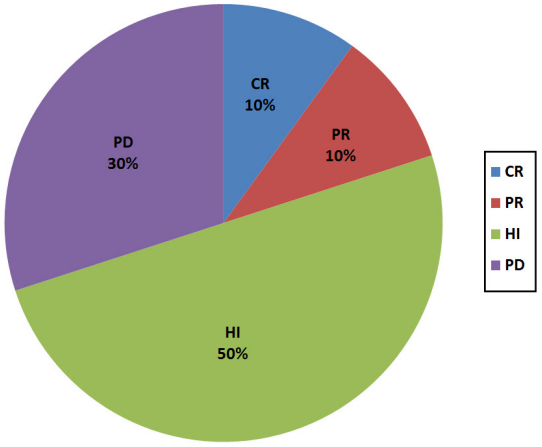

Fig.2.Response

Response was observed in 66,6% (4 of 6 patients) with MDS and in 75% (3 of 4 patients) with AML. The patients who did achieve a response had decreased transfusion requirements. Complete hematological response was observed in one case with RAEB 1 and 12 monosomy.

The most important effect of treatment was the increase in the quality of life, due to decrease of transfusional demand. The overall response to 5-Aza was heterogeneous, with no significant differences regarding blast percentage.

Follow-up cytogenetic data were not available.

From 10 patients treated with AZA, 4 patients died (40%): 3 died due to progression disease, (2 with MDS and one with AML), and one patient, with MDS, stopped treatment after 6 cycles, with HI, and died after one year without treatment, due to AML transformation. The median overall survival period of these 4 patients was 10,5 months (range 0,3 -18 months).There was a statistically significant overall survival difference between responders and non responders: 18 months versus 9 months (range 0,3 - 15months) (Fig. 3). The median survival rate for patients with MDS was11 months (range 0,4 - 18months) compared with 3 months for the AML patient with.

The remaining 6 patients are still in treatment with 5 Azacitidine.

All patients had a good tolerance to therapy, without significant adverse events.

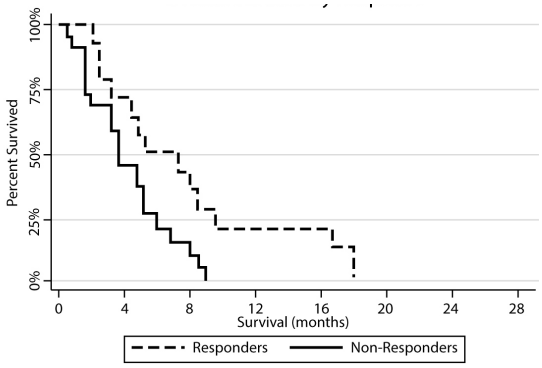

Fig. 3. Overall Survival by Response

Discussion

Treatment decisions in MDS are based on pathology, or a prognostic scoring system appropriated as a default staging system, and is now incorporated into drug labelling. Higher-risk myelodysplastic syndromes (MDS) are defined by patients who fall into higher-risk group categories in the original or revised International Prognostic Scoring System. Survival for these patients is critical, and treatment should be initiated rapidly. Standard therapies include hypomethylating agents: azacitidine and decitabine, which should be administered for a minimum of 6 cycles and continued for as long as a patient is responding. Also, awirching drugs is not recommendable (eg, administering decitabine in a patient whose disease is not responding to azacitidine)[14].

An epigenetic approach to therapy seems to be biologically justifiable in the treatment of MDS and AML because aberrant methylation was demonstrated in these diseases.Both azacitidine and decitabine are incorporated into DNA and produce a marked decrease in the activity of DNA methyl transferase [1,15].

DNA methylation occurs at the 5'-position of cytosine in areas of CpG dinucleotide islands, resulting in silencing of gene expression. DNA methyltransferase 1 (DNMT1) maintains existing methylation patterns after DNA replication, whereas members of the TET protein family remove methyl groups from CpGs. His tones undergo post translational modifications, leading to activation or repression of gene expression[14,16,17,18]. MDS patients generally exhibit genome-wide hypomethylation andCpG island hypermethylation, which results in genetic instability typical of cancer and tumor suppressor genes silencing. The hypomethylating agents are azanucleosides that act through proteosomic destruction of DNA methyltransferase and resultant chromatin decondensing. This results in depletion of DNA methyltransferase and theoretical reversal of the aberrant methylation that silences tumor suppressor genes, which is more common in higher risk MDS [14,19,20]. They also upregulate key regulators of late myeloid (CEBPE) differentiation and induce cell cycle

exit associated with upregulation of p27/CDKN1B, the cyclin-dependent kinase inhibitor that mediates cell-cycle exit by differentiation[14,21,22,23,24].

Initial reports of efficacy of hypomethylating agents came from studies on MDS patients. Azacitidine was approved by the US Food and DrugAdministration (FDA) for all MDS subtypes based on a phase 3 trial in which it was compared with supportive care [25]. Response rates to azacitidine were 14% (complete and partial), and 30% hematologic improvement, when analyzed using the International Working Group criteria. There was a significant delay in transformation to acute myeloid leukemia (AML) or death but a significant prolongation of survival in the treatment arm [14,26]. Azacitidine was furher explored in a phase 3 European trial confined to higher-risk MDS patients randomized to receive the drug or conventional care, which included best supportive care, low-dose cytarabine, or AML-type induction chemotherapy, as selected by investigators before randomization[14,27]. With a median follow-up of 21.1 months, median overall survival was 24.5 months vs 15 months for patients on the azacitidine vs conventional care arms (hazard ratio [HR] 0.58, P 5 .0001)[14].

Similar to azacitidine, decitabine received FDA approval based on a phase 3 study in all MDS subtypes in which patients were randomized to the drug or to receive supportive care [28]. Based on International Working Group criteria, complete and partial responses occurred in 17% of patients, and hematologic improvement occurred in 13%. There was no significant delay in AML transformation or death for decitabine-treated patients [14]. A phase 3 European study was then conducted, in which higher-risk MDS patients were randomized to decitabine or to best supportive care [29]. Although the complete and partial response rate was 23%—similar to that with azacitidine—there was no survival advantage for decitabine vs supportive care, with a median survival of 10.1 vs 8.5months, respectively (HR 0.88, P5.38)[14,29].

Conclusions

All patients from our lot had a good tolerance to therapy, without significant adverse events. The overall response to 5-Aza was heterogenous, with no significant differences regarding blast percentage, with one complete response in the case with 12 monosomy. Unfortunately in 3 patients with AML, treated with Decitabine, there was a delay in the time of treatment initiation due to administrative and financial issues, which led to their death caused by disease progression. There were no side effects.

The presented data indicate similar results to that in literature. The most important effect of treatment was on the quality of life, by the reduction in the transfusional demand. Hypomethilating agents are a less toxic alternative to classical cytotoxic/antimetabolites agents.

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