Farm Hosp. 2010;34(4):204–208

Farmacia HOSPITALARIA

www.elsevier.es/farmhosp

BRIEF REPORT

Effectiveness and safety of 5-azacitidine in three patients with myelodysplastic syndromes

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Received June 29, 2009; accepted November 10, 2009

KEYWORDS
5-azacitidine;
Myelodysplastic syndrome;
Effectiveness;
Safety;
Quality of life

Abstract
Objective: To assess the effectiveness and safety of using 5-azacitidine to treat myelodysplastic syndromes.
Methods: Review of medical records of patients who received 5-azacitidine 75 mg/m2 subcutaneously for during 7 days every 28 days in twelve cycles as compassionate use. We evaluated the objective response, clinical improvement and time to disease progression. We recorded adverse reactions described in the medical history.
Results: Six patients were candidates for treatment with 5-azacitidine. Three cases were evaluated over the study period. Most remained in partial response or better after the study, and no longer needed transfusions. In one patient, the treatment appeared to delay progression to leukaemia.
Conclusions: 5-Azacitidine might be considered an effective and relatively safe drug, and may have contributed to controlling peripheral cytopenias, improving the quality of life and delaying progression to leukaemia. Additional studies with more patients are needed to support these results.

PALABRAS CLAVE
5-Azacitidina;
Síndrome mielodisplásico;
Efectividad;
Seguridad;
Calidad de vida

Efectividad y seguridad de 5-azacitidina en tres pacientes con síndrome mielodisplásico

Resumen
Objetivo: Evaluar la efectividad y seguridad del tratamiento con 5-azacitidina en síndrome mielodisplásico.
Métodos: Revisión de historias clínicas de pacientes que recibieron 5-azacitidina 75 mg/m2 subcutánea durante 7 días, cada 28 días en 12 ciclos. Se valoró la respuesta objetiva, mejoría clínica y tiempo hasta la progresión de la enfermedad. Se recogieron las reacciones adversas descritas en la historia clínica.

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1130-6343/$ - see front matter

Resultados: Seis pacientes fueron candidatos a tratamiento con 5-azacitidina. Tres casos fueron evaluables tras el período considerado. La mayoría permanecieron en respuesta parcial o mejor al finalizar el estudio, dejando de precisar transfusiones. En una paciente se retrasó la progresión a leucemia.

Conclusiones: 5-Azacitidina podría considerarse un fármaco relativamente efectivo y seguro, pudiendo haber contribuido al control de citopenias periféricas, a mejorar la calidad de vida y a retrasar la progresión a leucemia. Serían necesarios estudios con mayor número de pacientes que corroborasen estos resultados.

Introduction

Myelodysplastic syndromes (MDS) are a group of conditions characterised by the regular presence of normo or hypercellular bone marrow (BM), morphological dysplasia, ineffective haematopoiesis, which determines the development of peripheral cytopenias, and a high risk of becoming acute myeloid leukaemia (AML).[1]

The diversity in prognoses and the advanced age of most patients make the choice of treatment difficult; allogeneic haematopoietic stem cell transplantation (allo-HSCT) is the only effective treatment,[2,3] even when it can only be applied to a small number of patients.

Fever and weight loss are unusual and they are typically associated with the development of the disease, which causes bone marrow failure in most patients and death as a result of bleeding or infection.[4] Its evolution to AML is linked to a poor prognosis. Usually, patients who suffer from refractory anaemia (RA) or refractory anaemia with ringed sideroblasts (RARS) are at less risk of this developing into AML than patients with refractory anaemia with excess blasts (RAEB) or refractory anaemia with excess blasts in transformation (RAEB-T).[5]

The objectives when treating MDS are to control the symptoms of cytopaenias, improve the quality of life, delay its evolution towards AML and generally to prolong life. The standard treatment to date had been supporting care (observation, the use of antibiotics to control infections and red blood cell and platelets transfusions).[6] Some patients have also been treated with colony stimulating factors, as well as recombinant human erythropoietin.

During the last few years, scientific advance and a better understanding of the physiopathology of MDS have resulted in the discovery of new treatment targets[6] and the development of new drugs.

5-Azacitidine is the first of a new type of antineoplastic drugs, administered by injection, known as hypomethylant agents. Its efficiency was tested in 3 studies conducted by the Cancer and Leukaemia Group B (CALGB),[7-9] during which 75 mg/ m^2 were given over 7 out of every 28 days. The results of these clinical tests (CT) showed that 5-azacitidine reduced the cytopaenias associated with MDS, delayed the development of leukaemia, improved the quality of life and extended life in the majority of patients treated.[10]

The objective of this study is to establish the efficiency and safety of this new drug in patients suffering from MDS who, due to their individual characteristics (age, clinical state, concurrent conditions, etc.) are not suitable for treatment with allo-HSCT.

Method

An observational, longitudinal and retrospective study was planned to last for a period of 19 months.

All patients who had been treated for RAEB-subtype MDS with 5-azacitidine were selected from computer records supplied by the central unit for the manufacture of cytostatic drugs and obtained using the Oncofarm® software. A 75 mg/ m^2/ day dose was administered subcutaneously during 7 out of every 28 days, for a total of 12 cycles.

The appropriate clinical histories were reviewed and the following variables collected: age at the time of the diagnosis, sex, RAEB-subtype MDS diagnosis (confirmed prior to joining the study), dosage schedule, background, previous treatments, clinical evolution and adverse reactions.

The response criteria being assessed are shown in Table 1. In addition, progress of the disease over time was also measured. The reference values used for haemoglobin (Hb), leukocytes and platelets were 12-16 g/ dl, 4-11 x 10^3/ µl and 150-500 x 10^3/ µl respectively.

Response to treatment was assessed every 4 cycles. Toxicity was measured using version 3.0 of the Common Terminology Criteria for Adverse Events (CTCAE)[11] classification from the National Cancer Institute (NCI). The criteria to grade the toxicity appearance time were: immediate, early, delayed or late.

Table 1 Response criteria

	Peripheral blood	Bone marrow
CR (duration ≥4 wks)	Absence of blasts. Full normal count*	<5% blasts
PR (duration ≥4 wks)	Absence of blasts. Recovered by ≥50%*	Decrease ≥50% blasts

CR indicates complete response; PR, partial response; wks, weeks.
*In relation to normal values of baseline levels of haemoglobin, leukocytes and platelets.

Results

During the actual period of study, 5-azacitidine was given to 6 patients (average age=70 years). 3 patients were excluded, one due to lack of response to treatment after 4 cycles, and two for non-completion of the first 4 cycles.

Case 1

62-year old female, studied for severe thrombopenia and intermediate-2 RAEB-subtype MDS, which was diagnosed in 2006. She initially showed 8% myeloid blasts with normal cytogenetics without fever.

A few months before the start of the treatment with 5-azacitidine (not having received either lenalidomide or intensive chemotherapy previously), she required 13 transfusions of platelet concentrate (PC) and showed 17% blasts in BM.

The patient showed a general improvement once the treatment with 5-azacitidine had started and her levels of Hb increased slightly. The platelet response was variable, almost reaching the lower limit of the reference range. The leukocyte readings remained within the measured range. At the end of the period, the response was higher than the PR (6% blasts in BM with normal peripheral cytopaenias); no further transfusions were necessary and her general condition improved. No blasts were found in peripheral blood.

Following the second cycle, the patient showed an early type I skin reaction and type I haematoma around the puncture areas. She required a transfusion of platelets, which gave good results. After cycles 10 and 11 her clinical state remained good, but there was occasional itching. The period of study ended without fever or bleeding being observed and the patient in a perfect general condition.

Case 2

Sixty-six-year old female, studied in 2002 for thrombopaenia. She was diagnosed with intermediate risk RAEB-subtype MDS, showing peripheral cytopaenias. The patient remained without symptoms and required no treatment, however, there was a development in her haematological process that revealed neutropaenia and thrombopaenia.

In 2006 she was diagnosed with high risk RAEB-subtype MDS and commenced treatment with 5-azacitidine (not having received either lenalidomide or intensive chemotherapy previously). A small increase in the levels of Hb was recorded, at around the lower limit of the range measured. The number of leukocytes remained close to the lower limit of the range throughout the period of study. The platelet response was very slight and their level was far below normal values.

The results of the evaluation conducted after the fourth cycle did not meet the criteria of complete response (CR) given that, despite having reached 4% blasts in BM (initially 13%), normal peripheral cytopaenias were not achieved. Subsequently this response decreased, but there was an increase in the number of blasts after the eighth cycle. No blasts were found in the peripheral blood during the period of study.

The patient completed the period of study without symptoms. She did not meet the criteria of either partial response (PR) or CR, although a progression to AML was observed, which would indicate that there was some response to the treatment.

Following the first cycle, she suffered an early type-II local skin reaction (which required treatment with paracetamol) and type-I haematoma around the puncture areas; these persisted throughout the study. From the sixth cycle onwards, she occasionally showed a clinical profile of early type-I diarrhoea and constipation but these were resolved without problems.

Case 3

Sixty-nine-year old male showing a progressive clinical profile of weakness and breathlessness during one month, as well as pancytopaenia. In 2006, medullar and cytogenetics tests gave a diagnosis of intermediate-1 risk RAEB-subtype MDS. He suffered from acute asthenia accompanied by severe cytopaenias (anaemia, neutropaenia and thrombocytopaenia) and required a large number of transfusions (48 CH and 69 PC) and colony-stimulant factors (filgrastim). The first medullar tests carried out in 2007 showed normo-cellular BM with 12% myeloid blasts and a normal cytogenetics.

Treatment with 5-azacitidine commenced, (together with filgrastim and PC and CH transfusions during cycles 1 and 2), without being given lenalidomide or intensive chemotherapy previously. After the first cycle, the asthenia disappeared and his general condition was considered satisfactory. Following the second cycle, transfusions were no longer necessary, the number of platelets increased, haemoglobin levels recovered significantly and the patient showed an excellent general condition. Filgrastim was required during the sixth cycle. The three series were recovered without further transfusions or colony-stimulant factors.

The myelogram performed after the eighth cycle revealed 4% blasts (initially 12%) and normal peripheral cytopenias, which demonstrated that CR was achieved after 32 weeks of treatment; this response was sustained after the end of the study (3% blasts and peripheral blood tests results stable). No blasts were found in the peripheral blood and the patient continued to show no symptoms and a perfect general condition.

After the sixth cycle a diarrheic profile appeared and was treated without problems. There was no evidence of local reactions and the general level of tolerance was very good.

Discussion

This work studies the effectiveness and safety of 5-azacitidine in 3 patients with RAEB-subtype MDS.

It is a known fact that clinical tests (CT) provide a large amount of information that broadens our understanding of drugs. However, this information is even greater when the drugs are used under certain conditions, which help overcome their limitations (strictly chosen populations, a special relationship between patient and physician, greater involvement of the patient in terms of commitment to the treatment, etc.).

There have been no similar studies on 5-azacitidine published in our area, since it is the first antineoplastic drug

approved as monotherapy for the treatment of MDS. In addition, 5-azacitidine provides a new mechanism of action and has only recently been put on the market, therefore there is only a limited experience of its use. Nonetheless, its monitoring has been conducted over a long period of time.

However, this study has only been carried out on a small patient sample and therefore cannot offer significant results. Moreover, there is no random assignment or control group, although it could provide data on effectiveness and safety in specific cases, which would aid the understanding of the profile of 5-azacitidine after marketing.

The patients studied showed characteristics comparable to those used in the pivotal clinical tests,[8,9] similar average age[8] (67.3 years), the presence of anomalies in 2 or 3 cell lines (under base conditions) and a large number of blasts in BM. They had all been diagnosed with RAEB-subtype MDS prior to their inclusion in the study. Two of them required a large number of transfusions (one also needed to be given colony-stimulant factors), and another showed a high risk of leukemic transformation. From the fourth cycle onwards, the patients experienced a reduction in the percentage of blasts present in BM (as was also found by Silverman et al[8]) and an increase in the level of platelets, Hb and leukocyte count. As was the case with these authors, patients 2/3, who relied on transfusions, no longer needed them during their partial or complete response.

In concurrence with the said authors, most patients (2/3) remained in PR or better at the completion of the study. Also, one third of patients sustained CR for at least 12 weeks.

In addition, the one patient who did not achieve the CR criteria after using 5-azacitidine, did show a response higher than PR, had no further need for transfusions and her general condition improved significantly, as did her quality of life. This result was similar to others obtained by Kaminskas et al[12] in subsequent tests.

It should be emphasised that, in another patient with high risk of leukemic transformation (1/3), the possible onset of AML was delayed (up to this date it still has not been diagnosed), despite her not having reached the PR or CR criteria. This is a very positive fact, which could be attributed to the beneficial effects of the treatment with 5-azacitidine and was also observed by Silverman et al.[13]

Moreover, it is very significant that one of the patients achieved a sustained CR and no longer required the initial high levels of transfusion or colony-stimulant factors and his clinical profile evolved from severe asthenia to a perfect state of wellbeing by the end of the study. This change had a very positive effect on his quality of life. Other authors have experienced similar results.[8,14]

With reference to safety, the use of 5-azacitidine had very few side effects, as was also observed by Sullivan et al.[5] Any adverse reactions presented have already been explained in the CT above; there was a frequent local reaction at the puncture points between the first and fourth cycles, with the exception of one patient, who in addition to this, showed haematoma that persisted throughout the period of study.

In the light of the results obtained, 5-azacitidine could be rated as a highly effective and safe medication in the patients studied, as it could have aided the control of their cytopenias symptoms, improved their quality of life and delayed the progression of AML, although it would be necessary in the future to conduct further studies over longer periods and including a larger number of patients, such as those recently carried out in other areas.[15] These would enable the collation of statistically meaningful data that would establish the real impact of 5-azacitidine on the general survival rate.

Conflict of interest

The authors state that they have no conflict of interests.

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