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A phase II Open-label Study of the Intravenous Administration of Homoharringtonine in the treatment of Myelodysplastic syndrome

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Abstract

Homoharringtonine is an alkaloid inhibitor of protein synthesis with activity in myeloid malignancies. We report a phase II pilot study of homoharringtonine in myelodysplastic syndrome (MDS). Induction consisted of homoharringtonine at 2.5 mg/m² via continuous infusion for seven days. Maintenance was given every 4 weeks. Nine patients were enrolled: five with refractory anaemia with excess blasts, two with refractory anaemia with excess blasts in transformation, one each with refractory anaemia and chronic myelomonocytic leukaemia, respectively. Median age was 70 years (55–84) and 6 (66%) were male. Per International Prognostic Scoring System (IPSS) two patients were intermediate-1, five intermediate-2 and two high-risk. Median chemotherapy courses were one (1–3). One patient (11%) responded with complete hematologic and cytogenetic remission after one course. Eight patients did not respond (four had stable disease, two progressed to acute leukaemia and two died during induction - from aspergillus pneumonia and intracerebral haemorrhage, respectively). Grade 3/4 myelosuppression seen in 56% (5/9). Serious non-hematologic toxicities included one case of grade 4 left bundle branch heart block and one grade 3 nephrotoxicity. Median time between courses was 42 days (35–72 days). In conclusion homoharringtonine might have clinical activity in some patients with MDS.

Keywords

Myelodysplastic syndrome; homoharringtonine; omacetaxine; response; toxicity

Introduction

Myelodysplastic syndromes (MDS) are a group of haematological disorders characterized by progressive cytopenias and a risk of transformation to acute myeloid leukaemia (AML). Treatment depends on the clinical status of the patient, and can range from careful observation and supportive care to induction treatment with AML-like chemotherapy. The prognosis of patients with high International Prognostic Scoring System (IPSS) score (intermediate-2 and high-risk disease) has been dismal, with poor disease-free and overall survival (Abdulhaq and Rossetti, 2007, Atallah and Garcia-Manero, 2008, Greenberg et al., 1997). Traditionally, treatment with high dose chemotherapy yields a low remission rate and high morbidity (Abdulhaq and Rossetti, 2007). Hypomethylating agents (5-azacitidine and decitabine) have become standard therapy improving outcomes over best supportive care or chemotherapy (Fenaux et al., 2009, Kantarjian et al., 2006, Silverman et al., 2002) and

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studies with 5-azacitidine have demonstrated a survival benefit compared to standard therapies (Fenaux et al., 2009). However, these agents are not considered curative and patients with disease resistant or refractory to hypomethylating agents have a poor prognosis and no available treatment options (Jabbour et al., 2010). Allogeneic stem cell transplant remains the only curative approach (Chang et al., 2007, Cutler et al., 2004), but a significant number of patients are not candidates for transplant as most patients diagnosed with MDS are over the age of 70 with multiple comorbidities or do not have suitable stem cell donors. Even if allogeneic stem cell transplant is available, using effective chemotherapy to reduce the percentage of bone marrow blasts prior to transplant may improve transplant outcomes (Barrett and Savani, 2008).

Homoharringtonine is a cephalotaxus alkaloid obtained from the evergreen tree *Cephalotaxus harringtonia* (Grem et al., 1988a). Homoharringtonine is a cell-cycle specific chemotherapeutic agent, effecting predominantly cells in G1 and G2 phase (Baaske and Heinsteins, 1977). Potential mechanisms of action of homoharringtonine include degradation of polyribosomes, early release of completed protein chains and competitive inhibition of protein synthesis by preventing substrate binding to the 60S ribosome subunit (Kantarjian et al., 2001, Huang, 1975, Fresno et al., 1977, Tujebajeva et al., 1989). Studies have also shown a myeloid differentiation effect (Kuliczowski, 1989, Boyd and Sullivan, 1984, Zhou et al., 1990) and an apoptotic effect in leukemic cells through unchaining of endoplasmic reticulum stress response and liberation of caspase (Boyd and Sullivan, 1984, Jie et al., 2007, Yinjun et al., 2004, Zhou et al., 1990, Takemura et al., 1985).

Homoharringtonine has shown clinical efficacy in myeloid malignancies. Homoharringtonine showed encouraging results in patients with chronic myeloid leukaemia who had failed prior interferon therapy (Visani et al., 1997, Quintas-Cardama and Cortes, 2008a, O'Brien et al., 1993, O'Brien et al., 1995). Initial studies from China showed response rates of 10–25 % in patients with AML (Kantarjian et al., 2001, Grem et al., 1988b). Further studies in the United States confirmed response rates of 10% to 20 % in AML (Feldman et al., 1992b, Warrell et al., 1985). Other studies implementing higher doses showed response rates of 15% to 30 % in patients with MDS and AML, albeit with increased toxicity and induction mortality (Feldman et al., 1996, Kantarjian et al., 2001). We report the results of a pilot phase II clinical trial of homoharringtonine in MDS conducted at MD Anderson Cancer Centre, Houston, USA (MDACC).

Methods

Inclusion and Exclusion Criteria

Patients 16 years or older diagnosed with primary or secondary MDS according to French-American-British (FAB) classification (including following subsets: refractory anaemia [RA], refractory anaemia with ring sideroblasts [RARS], refractory anaemia excess blasts [RAEB], refractory anaemia with excess blasts in transformation [RAEB-t] and chronic myelomonocytic leukaemia [CMML]) were eligible. Patients with therapy-related MDS (t-MDS) should have been cancer free for three years and have not received radiation or chemotherapy within the last six months. Patients must have a bone marrow consistent with MDS in the six weeks preceding the first study treatment. Eligible patients were required to have haemoglobin ≥ 10 g/dl (independent of red blood cells transfusions), symptomatic anaemia requiring red blood cells transfusions for at least three months, thrombocytopenia with two or more platelet counts $< 50 \times 10^9$ K/UL or significant clinical haemorrhage requiring platelet transfusions, absolute neutrophil count $< 1.0 \times 10^9$ K/UL or an MDS IPSS classification of either intermediate-2 or high risk. Patients were required to provide written informed consent prior to any study related procedure. A performance status of 0–2 according to the Zubrod scale and a life expectancy of greater than six weeks were required.

Pregnant and lactating females were excluded. Patients with New York Heart Association (NYHA) class III or IV heart disease, active ischemia or any uncontrolled, unstable cardiac conditions were excluded. Patients were required to have SGPT (ALT) and SGOT (AST) 2.5 times the upper limit of normal, bilirubin 2.5 times the upper limit of normal and creatinine 2.0 mg/dL. Patients with prior exposure to homoharringtonine or patients with acute leukaemia (> 30% blasts) were excluded. Patients who had received azacytidine, decitabine, cytarabine or investigational therapy in the 30 days preceding the first dose of study therapy were excluded. Similarly, patients who had received systemic chemotherapy in the 4 weeks prior to first dose of study drug were excluded. The protocol was approved by the Institutional Review Board and all patients signed an institutional review board-approved informed consent.

Treatment schedule

Patients received homoharringtonine at 2.5 mg/m² by continuous 24-hour intravenous infusion daily for seven days. This was repeated every four weeks until complete remission. Homoharringtonine dose could be increased to 3 mg/m² for patients who had no response or progression. If complete remission was not achieved by day 42 or if prolonged myelosuppression developed during any course, subsequent courses could be reduced to six days or less at the discretion of treating physician. Maintenance therapy consisted of homoharringtonine at 2.5 mg/m² daily for seven days (or fewer days if required for myelosuppression). This could be repeated every four weeks for up to 12 months or until treatment failure. Patients could be taken off study if they failed to achieve complete remission after three courses of homoharringtonine or if unacceptable toxicity developed at any point.

Evaluation

Treatments could be administered in hospital or in an ambulatory setting via portable intravenous infusion pump. Vital signs were recorded prior to and 30 minutes after commencement of each infusion and at completion of each course. In addition, during the first treatment course, vital signs were obtained at 24–48 hours and 72–96 hours from initiation of the infusion. Complete blood count, electrolytes, and serum chemistry were obtained three days prior to, and at the completion of each infusion. Patients had medical evaluations between courses at the discretion of the treating physician. Bone marrow examination and cytogenetics were performed at the end of the first cycle and every 3–4 months while on study or as clinical indicated.

Safety and Response Criteria

Complete remission, partial remission, stable disease, failure, relapse, disease progression, disease transformation, cytogenetic response and haematological improvement were defined according to criteria established by the International Working Group (IWG). (12). Cytogenetic response required 20 analysable metaphases. For the purpose of this analysis, a complete cytogenetic response was defined as no detectable cytogenetic abnormalities in patients with underlying cytogenetic abnormalities at baseline, and minor response required a 50% or more reduction in abnormal metaphases. Overall response rate was defined as complete remission plus partial remission. The overall clinical improvement was based on the proportion of patients achieving complete remission, partial remission and haematological improvement. The study was designed with a Simon two-step design (Liu et al., 2010). Interim analyses were planned after accruing 9 and 18 patients respectively. The study would be stopped if the ratio of overall response / treated patients was lower than 0/9 or 2/18, respectively. Adverse events were classified according to the National Cancer Institute Common Toxicity Criteria (version 2.0)

Results

Patients

The study was conducted between August 2003 and November 2003. A total of nine patients were enrolled. Table 1 summarizes the patient characteristics. Five patients had refractory anaemia with excess blasts, two patients had refractory anaemia with excess blasts in transformation and one patient each had refractory anaemia and chronic myelomonocytic leukaemia RAEB, respectively, according to French-American-British (FAB) classification. Three patients had a history of prior malignancy. Of these one had received radiotherapy for cervical carcinoma and two had received chemotherapy for colon cancer and breast cancer, respectively. One patient had been diagnosed with myeloproliferative disorder 6 years prior to enrolment on our study. He was initially treated with hydroxyurea for two years, but eventually evolved to MDS refractory anaemia with excess blasts. One patient was initially diagnosed as atypical chronic myeloid leukaemia and had been treated with imatinib and hydroxyurea for six months. Of the remaining patients, three patients had been treated with thalidomide plus antithymocyte globulin, tipifarnib, and decitabine, respectively. Three patients were dependent on red blood cell transfusion and no patients required platelet transfusions at time of enrolment. Overall, 1 patient had prior treatment with hypomethylating agents, 2 had prior treatments with arsenic, 1 had prior treatment with imatinib, 1 had prior treatment with a farnesyl transferase inhibitor and 1 had prior treatment with thalidomide. The median time from diagnosis to start of treatment with homoharringtonine was 17 months (range; 2–72 months).

Efficacy

One patient (11%) achieved an objective response (namely complete remission). This patient had refractory anaemia with excess blasts, transfusion dependent, with trisomy 8 and intermediate-2 IPSS score. Prior therapy included decitabine for 8 cycles, followed by arsenic trioxide for 90 days. He achieved complete remission with complete cytogenetic response (0% metaphases with trisomy eight, from 100% at baseline) on day 66 of the first course of homoharringtonine. After the second course, the patient relapsed with an increase in the bone marrow blasts to 15% and recurrence of the aforementioned cytogenetic abnormality. The response lasted 65 days. In addition, a transient improvement in blasts was observed in a patient with chronic myelomonocytic leukaemia. At baseline this patient had 18% bone marrow blasts with a pseudodiploid clone, with del (7q), t (13;21), del (5) and high-risk IPSS score. She had a decrease in bone marrow blasts to 8% after two courses of homoharringtonine, but she did not meet International Working Group criteria for hematologic improvement. Per International Working Group she was categorized as a failure and taken off study after the third course, since she had no further response. The other 7 patients were deemed treatment failures, including three patients with stable disease and no haematological improvement, two patients (one refractory anaemia with excess blasts in transformation and one refractory anaemia with excess blasts, respectively) that progressed to acute myeloid leukaemia after the first course, and two patients that died during induction (see adverse effects). No patient had an increase in dosage to 3 mg/m². The median number of courses administered was one (range, 1–3 courses).

Adverse Effects

Two patients were not able to complete seven days of the first course. One developed a left bundle branch block during the sixth day of infusion. He later developed worsening dyspnoea, hypoxemia and required intubation. The second patient developed renal toxicity, with a grade 3 elevation in creatinine on the fifth day of infusion. She developed aspergillus pneumonia and fatal myocardial infarction. Both patients had multiple comorbidities, including diabetes mellitus, hypertension and a history of cardiac problems. The first patient

received a second seven-day cycle without any complications. Other non-haematological side effects are noted in Table 2. Four patients had grade 3 or 4 neutropenia and five patients had grade 3 or 4 thrombocytopenia before entering study. Myelosuppression post-therapy was graded according to the modified criteria for patients with bone marrow disease before treatment; as specified in the Common Toxicity Criteria for Adverse Events (CTCAE Version 2.0). A total of 5 patients had grade 3/4 myelosuppression (56%). Four patients had grade 3 neutropenia and one patient had grade 4 neutropenia. Of the four patients with grade 3 neutropenia three had concomitant grade 3 thrombocytopenia and one had concomitant grade 4 thrombocytopenia (Table 3). The refractory grade 4 thrombocytopenia was seen in the patient with chronic myelomonocytic leukaemia, who had response to therapy with decrease in blast percentage after two courses of homoharringtonine as described in previous paragraph. She received frequent platelet transfusions over 3 weeks and ultimately died from intracerebral haemorrhage on day 35 of course one. She had a platelet count of $43 \times 10^9/L$ before starting homoharringtonine. The median time between each course, for those who received more than one course was 42 days (range 35–72 days). Two patients required a decrease to five days per course due to prolonged myelosuppression after the first course.

Discussion

In this study we observed an overall response rate of 11% in MDS patients treated with homoharringtonine. This is in accordance with previously reported responses rates of 8% to 28% in acute myeloid leukaemia and MDS patients treated with single agent homoharringtonine (Kantarjian et al., 2001, Bian et al., 1990, Li et al., 1983, Warrell et al., 1985, Feldman et al., 1996). Of note, most of these studies administered higher doses and included mostly patients with acute myeloid leukaemia rather than MDS (Kantarjian et al., 2001, Kantarjian et al., 1989, Tan et al., 1987, Feldman et al., 1992a). Interestingly, one of our patients achieved a complete remission with complete cytogenetic response after one course of homoharringtonine. This patient had refractory anaemia with excess blasts and had lost response to previous treatment with decitabine. He did not have significant complications during induction phase, but later developed prolonged myelosuppression and required a decrease to five days of homoharringtonine for course two. He progressed 63 days after initial response.

Two serious non-haematological events were noted with homoharringtonine. One patient developed an arrhythmia and cardiac failure that required intubation. The second event consisted of an elevated creatinine in a patient with diabetes mellitus and past history of myocardial infarcts. Cardiovascular toxicity related to homoharringtonine has been noted in other studies, but it usually manifests as hypotension (Kantarjian et al., 2001, 1976, Coonley et al., 1983, Feldman et al., 1992b). The patient who developed arrhythmia had a history of cardiomyopathy, arrhythmias and an implanted defibrillator. These may have increased his susceptibility to homoharringtonine cardiotoxicity, resulting in ventricular arrhythmia. However, this patient was able to receive a second cycle of homoharringtonine at a reduced dose without any complications. It is therefore difficult to assess whether the toxicity was truly attributable to homoharringtonine. As anticipated, haematological toxicities were frequent. All patients developed myelosuppression, although all had decreased peripheral blood counts at baseline. Two patients died of myelosuppression-related complications. One patient died of fungal pneumonia and the second patient died of intracerebral haemorrhage from refractory thrombocytopenia. The median time to recovery between courses for patients who received more than one course was 42 days, which suggests a potent and prolonged myelosuppressive effect. However, one must take into account the advanced age of our patients (median 70 years) which may have contributed to the prolonged myelosuppression. We did not notice severe hyperglycaemia or hypotension which have

been noted with homoharringtonine in other studies (Kantarjian et al., 2001, Ajani et al., 1986, Warrell et al., 1985, Feldman et al., 1992a, Feldman et al., 1992b).

Currently the hypomethylating agents, azacitidine and decitabine are the only United States Food and Drug Administration (FDA) approved drugs for the treatment of MDS. These are the first agents to significantly decrease the rate of leukaemic transformation and improve overall survival in patients with high-risk MDS (Abdulhaq and Rossetti, 2007, Atallah and Garcia-Manero, 2008, Plimack et al., 2007). Although decitabine and azacitidine have altered the course of this disease in select patient populations (Fenaux et al., 2009, Kantarjian et al., 2006, Silverman et al., 2002, Kornblith et al., 2002), there remains an unmet need for novel effective agents in MDS. Homoharringtonine has been used either alone or in combination in patients with MDS or acute myeloid leukaemia. In spite of multiple studies a standard dose for homoharringtonine in MDS or acute myeloid leukaemia has not been established. Our dose is one of the lowest tested and produced results similar to studies with higher doses. Newer homoharringtonine semisynthetic formulations are currently being evaluated in clinical trials and are showing encouraging results in myeloid malignancies (Levy et al., 2006, Quintas-Cardama and Cortes, 2008a, Quintas-Cardama and Cortes, 2008b).

In conclusion, homoharringtonine at the doses used in this study has modest activity in MDS. However, some patients that have failed prior therapy with hypomethylating agents may respond to therapy with homoharringtonine. Further studies are required to identify the optimal dose schedule and the role this agent may have among patients who have failed prior hypomethylating agents.

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Table I

Patient Characteristics (N=9)

Characteristics	N (%) / Median [Range]
Age (years)	70 [55–84]
Male patients	6 (66%)
Median number of prior therapies	1 [1–3]
Transfusion dependent patients	3 (33%)
PS 1	6 (67%)
White blood cell count, $10^9/L$	2.7 [1.2 – 26.5]
Absolute neutrophil count, $\times 10^9/L$	1.2 [0–11.9]
Haemoglobin, g/L	9.3 [9.8 – 11.3]
Platelet count, $\times 10^9 /L$	33 [10.7 – 210]
Peripheral blasts %	0 [0–24]
Bone marrow blasts %	8 [1–21]
IPSS:	
Intermediate-1	2 (22%)
Intermediate-2	5 (56%)
High Risk	2 (22%)
MDS FAB Classification:	
RA	1 (11%)
RAEB	5 (56%)
RAEB-t	2 (22%)
CMML	1 (11%)

Abbreviations: IPSS = International prognostic scoring system; MDS = myelodysplastic syndrome; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; RAEB-t = refractory anaemia with excess blasts in transformation; CMML = chronic myelomonocytic leukaemia, PS = performance status

Table II

Non Hematologic Adverse effects (Number of events)

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increase			1	
Diarrhoea	1	1		
Dyspnoea				1
Febrile Neutropenia			2	
Haemorrhage				1
Hyperbilirubinemia	1			
Hyperglycaemia	1			
Hypoxia				1
Fatigue			1	
Headache	1			
Infection			1	1
Left bundle branch block				1
Stomatitis	1			
Nausea Vomiting			1	
Rash	1			

Table III

Hematologic Adverse Effects (Number of events)

	Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	2	5	0	
Neutropenia			4	1
Thrombocytopenia			3	1