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Darbepoetin alfa for the treatment of anaemia in alpha- or beta-thalassaemia intermedia syndromes

Thalassaemia intermedia (TI) patients have moderate to severe anaemia and frequently develop progressive complications. Consequently, substantial studies for improving the anaemia were carried out, mostly directed at augmenting fetal haemoglobin (HbF) synthesis.

Another approach has utilized the recombinant growth factor, recombinant human erythropoietin (rHuEPO) to stimulate proliferation of erythroid cells. (Rachmilewitz *et al*, 1995; Bourantas *et al*, 1997). This resulted in an increase in haemoglobin (Hb), but the relatively high cost and difficulty in administration discouraged the execution of subsequent studies. The new erythropoetic stimulating agent, darbepoetin alfa (DAR), has a longer half-life and could result in further sustained increase of Hb, but has been rarely used for thalassaemia patients.

The present study was carried out to assess the response to dose escalation of DAR in patients with TI phenotype and the capacity of responding patients to sustain the increase in Hb during treatment.

The study was approved by the institutional review board at Children's Hospital and Research Center at Oakland (#2002–11). TI patients aged ≥14 years, with a Hb ≤ 95 g/l who had not required a blood transfusion for ≥3 months, were enrolled (Table I). DAR (Aranesp; Amgen Inc., Thousands Oaks, CA, USA) was administered at 4·5 μg/kg/week for 8 weeks (equivalent to 20 000 u of rHuEPO three times weekly). For patients whose Hb did not increase by 15 g/l over baseline on two consecutive measurements 1 week apart, the dose was increased to 6·75 μg/kg/week for an additional 8 weeks. If Hb had not increased by the same criteria over baseline, the dose was further increased to 9·0 μg/kg/week for an additional 8 weeks. If, at the end of each 8-week phase, there was an increase in Hb of ≥15 g/l, DAR treatment was continued at the same dose for additional 16 weeks.

A complete blood count was performed every 2 weeks and after each dose adjustment. Levels of ferritin, serum iron, transferrin iron binding capacity (TIBC), transferrin receptor (sTfR), folate, vitamin B12, HbF and erythropoietin were measured at enrolment, at changes in DAR dose and while on a steady dose.

Statistical analysis was performed using SAS software (Cary, NC, USA). Bivariate Pearson correlations were computed between the various parameters. P values <0·05 were considered significant.

Ten patients with a mean baseline Hb level of 73 ± 1 (59–95) g/l received DAR at 4·5 μg/kg/week (9·5 ± 4·3 weeks) (Table I) and all showed increased Hb levels; mean 82 ± 13; 63–106 g/l ($P < 0·0001$) (Fig 1), although administration at 2-week intervals (10 ± 3·4 weeks) resulted in a 7 ± 6 g/l decline. A weekly dose of 6·75 μg/kg (12·4 ± 5·6 weeks), raised the Hb by 11 g/l

Table I. Clinical and laboratory characteristics of patients treated with darbepoetin alfa.

Pre-treatment characteristics										
Sex/age (years)	M/33	F/37	F/19	M/30	F/18	F/27	F/19	F/17	F/40	F/41
Thalassaemia type	β TI	β TI	β TI	E/β^0 thal	E/β^0 thal	β TI	α thal	E/β^0 thal	β TI	β TI
Genotype	IVS I-110/IVS I-110*	121 (G-T)/β	−28(AG)/CD 41/42*	17 (A-T) /E*	17 (A-T)/E*	cd110/HPFH*	Hb H-CS	17 (AT)/E	IVS1-6/ IVS1-6	−28 (A-G) /−28 (A-G)
Splenectomized	Y	Y	Y	Y	N	N	N	N	Y	Y
Prior transfusion/iron chelation	Y/Y	N/N	Y/Y	N/N	N/N	N/N	N/N	N/N	N/N	Y/Y
Prior Hb-inducing treatment/↑ in Hb ≥ 10 g/l	No	No	No	HC/no	HC/no HC + EPO/yes	HU	no	HC/no HC + EPO/yes	EPO + HC/some	EPO + HC/some
Baseline laboratory findings										
EPO (iu/l)	1674	166	160	29	128	488	73	49	113	196
sTfr (nmol/l)	210	114	126	64	80	207	140	178	111	na
HbF (%)	42	7	50	10·5	13·3	78	3	11	17	20
Ferritin (μg/l)	711●	296	4600●	605	170	323	210	208	470	1870●
Serum iron (μmol/l)	30·4	21·8	22·5	39·3	17·9	17·9	19·5	15·7	60·6	36·3
TIBC (μmol/l)	33	37·6	21·6	40·4	36·5	44·5	18·2	47·2	51·3	40·6
Haemoglobin response										
Baseline Hb (g/l)	59	75	76	95	72	78	68	83	67	65
Mean↑ in Hb on DAR (g/l)†	5	18	20	11	15	10	09	12	17	10
2 Peak Hb levels (g/l) on DAR	70/75	98/100‡	96/99‡	105/109	89/94‡	91/91	77/84	102/103‡	89/90‡	0/82‡

β TI, β thalassaemia intermedia; E/β^0 thal, E/β^0 thalassaemia; Hb H-CS, Hb H-constant spring; HC, hydroxycarbamide.

Oral iron supplementation was not given and iron chelation (●) was continued (n = 3).

*Presence of 1 or 2 alpha globin deletion.

†Best mean response to DAR at either 4·5 or 6·75 μg/kg weekly dose.

‡Increase in Hb > 15 g/l in two measures at least 1 week apart.

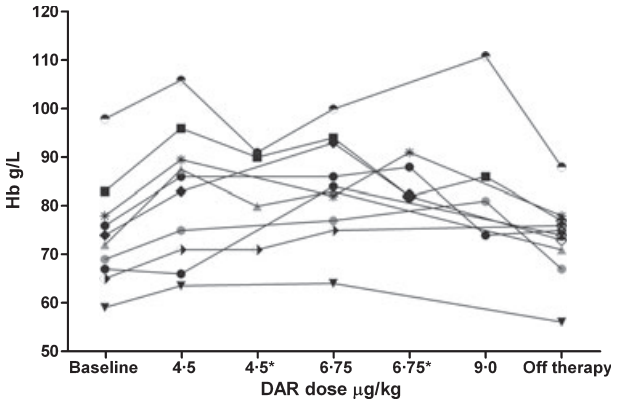

Fig 1. Individual patients' mean Hb on the various treatment doses administered once a week. *Indicates dose administered in 2-week intervals. Each patient is represented by a different symbol; few overlapping symbols were moved by 1·0–2·0 g/l to allow better examination of the data points.

from baseline to a mean of 84 ± 10 g/l, and by 13 ± 4 g/l in 6/10, but the same dose administered at 2-week intervals ($n = 5$; 9·6 ± 3·6 weeks) resulted in inconsistent response. Only 25% (1/4) of patients had an increase in Hb at a dose of 9 μg/kg/week. Haemoglobin returned to the pre-treatment range 2–4 weeks after DAR treatment was discontinued (Fig 1).

Pre-treatment Hb concentration predicted the increase in Hb using DAR doses of 4·5 and 6·75 μg/kg. ($r = 0{\cdot}9$ $P < 0{\cdot}0001$ and $r = 0{\cdot}9$ $P < 0{\cdot}0005$, respectively). Baseline EPO levels (median 126, range 49–1674 iu/l) had a negative correlation with Hb level when 4·5 μg/kg DAR was administered ($r = -0{\cdot}5$; $P < 0{\cdot}1$), approaching statistical significance at the 6·75 μg/kg dose ($r = -0{\cdot}7$, $P < 0{\cdot}02$). There was also a correlation between baseline EPO and HbF concentrations ($r = 0{\cdot}8$; $P < 0{\cdot}04$), but HbF as well as sTfR did not change significantly during DAR treatment (25·3 ± 22% and 26 ± 22% and 136 ± 52 and 130 ± 54 mmol/l, respectively). Absence of spleen did not have a significant effect on the Hb response to DAR.

Serum iron and ferritin levels decreased during treatment, from a baseline of 28 ± 14 to 23·6 ± 13 μmol/l and 947 ± 1380 to 744 ± 1100 μg/l, respectively. While treatment at the 4·5 and 6·75 μg/kg doses was well tolerated, DAR at 9 μg/kg caused bone pain in 2/4 patients. One patient, who also received rHuEPO prior to DAR, developed a sacral mass resulting from extramedullary haematopoiesis. Discontinuation of DAR treatment and 6 months of regular transfusions and hydroxycarbamide resulted in decrease of the mass size and concomitant pain relief.

Our preliminary results demonstrate the potential role of DAR for the treatment of moderate anaemia in TI patients, particularly in those with a low EPO level. Weekly DAR administration resulted in a sustained increase in Hb of ≥10 g/l in 80% and ≥15 g/l in 40% of the patients. Increasing the interval of DAR administration was not successful, suggesting a need for continuous stimulation to overcome the ineffective erythropoiesis and haemolysis.

EPO levels vary in thalassaemia and were found to be low for the degree of anaemia and to decrease with age (Galanello *et al*, 1994; Sukpanichnant *et al*, 1997; O'Donnell *et al*, 2007), resulting in reduced erythropoietic stimulation and increased apoptosis (Perrine, 2005); providing the rationale for this treatment. The role of DAR in treating symptomatic α thalassaemia patients needs further study; our patient with Hb H-CS had a modest response to DAR, suggesting that DAR stimulation of erythropoiesis may be insufficient to compensate for the higher rate of haemolysis. A positive effect of DAR has been reported, with >20 g/l increase in Hb, in a milder form of α thalassaemia, Hb H disease (Fortenko *et al*, 2009), as well as successful use in a pregnant woman with Hb H disease (Maccio *et al*, 2009).

Serum iron and ferritin concentrations decreased in our patients; possibly a result of increased mobilization of stored iron as effective erythropoiesis improved. Such reduction in iron stores was described following EPO-stimulated proliferation of erythroid precursors (Cermak, 2006); Therefore, in clinical practice, monitoring of iron stores and possible iron supplementation with continuous DAR treatment should be considered.

In summary, our results demonstrate a possible role of DAR for the management of anaemia in β TI; potentially decreasing morbidity and the use of transfusions. Due to the risk of marrow expansion, careful monitoring is indicated. Spine imaging prior to long term therapy and combined use of DAR and hydroxycarbamide, a drug known to reduce the excessive marrow expansion (Meo *et al*, 2008) could be considered.

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Phase I study of bortezomib plus ICE (BICE) for the treatment of relapsed/refractory Hodgkin lymphoma

Classical Hodgkin lymphoma (HL) is considered highly curable. However, 20% of patients develop relapsed or refractory disease and standard management is salvage chemotherapy followed by high dose chemotherapy with an autologous stem cell transplant (ASCT). Moskowitz *et al* (2001) treated relapsed HL patients with two cycles of ICE (ifosfamide, carboplatin, etoposide) and responding patients underwent ASCT. The event-free survival (EFS) at 43 months for those who underwent ASCT was 68%. Similar to other studies, superior outcomes were seen for those in complete remission (CR). Three factors were associated with poor outcomes: initial CR of less than a year or primary refractory disease, extranodal disease, and B symptoms. EFS ranged from 83% for patients with one risk factor to 10% for patients with three risk factors (Moskowitz *et al*, 2001). Recent studies also showed the impact of ^{18}F-fluoro-deoxyglucose (FDG)-positron emission tomography (PET) response on EFS (Filmont *et al*, 2007; Schot *et al*, 2007). These correlations support the need to further improve salvage chemotherapy response rates. One approach is through the addition of targeted agents to chemotherapy.

In HL cells the proteasome inhibitor bortezomib causes cell cycle arrest at the G_2-M phase and induces apoptosis (Zheng *et al*, 2004). In our pilot trial, 14 refractory HL patients were treated with bortezomib at 1·3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle. One patient had a partial response and two patients had stable disease (Younes *et al*, 2006). Three other clinical trials demonstrated similar outcomes in heavily pretreated HL patients (Blum *et al*, 2006; Strauss *et al*, 2006; Trelle *et al*, 2006).

Although single-agent bortezomib responses in HL were low, data from chemotherapy combination trials with bortezomib in non-small cell lung cancer and breast cancer have described positive results, thus suggesting that bortezomib can potentially act to overcome chemotherapy resistance. Therefore, we designed a phase I trial to evaluate safety and to test the hypothesis that the addition of bortezomib to ICE (BICE) would increase CR rate for relapsed/refractory HL patients.

Patients in this single centre study were enrolled between February 2007 and January 2008. Eligibility criteria included patients with first relapse or refractory classical HL who had received a front-line anthracycline-containing regimen. Patients underwent CT and PET scans prior to enrollment and after three cycles of BICE. CT scan response criteria were in accordance with 1999 International Workshop guidelines. Bortezomib was administered at dose-escalation levels of 1·0, 1·3, and 1·5 mg/m^2 on days 1 and 4. ICE was given according to standard regimen, pegfilgrastim was given on day 5 and patients received prophylaxis with ciprofloxacin, fluconazole, and valacyclovir. Treatment was administered on an inpatient basis every 14 d if the patients' absolute neutrophil count and platelet count had recovered to $\geq 1{\cdot}0 \times 10^9$/l and $\geq 100 \times 10^9$/l, respectively.