

Predicting erythroid response to recombinant erythropoietin plus granulocyte colony-stimulating factor therapy following a single subcutaneous bolus in patients with myelodysplasia

We randomized 21 patients with low-risk myelodysplastic syndromes (MDS) to receive a single subcutaneous bolus of recombinant erythropoietin (epoietin) ± granulocyte colony stimulating factor (G-CSF), or placebo and monitored erythropoietic response over 7 days. In this small study, the reticulocyte response at day 7 was highly predictive of subsequent response to a therapeutic trial of epoietin + G-CSF.

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Interventional therapy capable of relieving anemia in patients with low-risk myelodysplastic syndromes (MDS) is currently inadequate. Epoietin granulocyte colony-stimulating factor (G-CSF) is an effective therapy for selected MDS patients. Despite validated response prediction models, response rates are only 60% in the high predicted response group.¹

MDS patients with < 10% bone marrow blasts and a high or intermediate predicted response rate¹ were included in this study, which was approved by the Local Research Ethics Committees of NHS Tayside, NHS Lothian, and NHS Grampian. FAB subtypes were refractory anemia (RA)=11, RA with ring sideroblasts=9, RA with excess blasts=1. Twenty-one patients were randomized to receive a single subcutaneous bolus of active drugs or placebo (investigators blinded) for pharmacodynamic studies. Drug doses were G-CSF (Lenograstim) 263 µg subcutaneously on day 0, and Eprex (Ortho-Biotec) 20 000 U (Patient 1) or NeoRecormon (Roche) 18 000 U (subsequent patients). Placebo for NeoRecormon contained all carriers but no active drug (Roche) and for Eprex and Lenograstim was normal saline at an appropriate volume. Patients one and 2 were subsequently treated with Eprex 10,000 units thrice weekly (tiw) increasing to 20,000 units thrice weekly if no response at 4 weeks, and patients 3-21 (except patient 7) were treated with NeoRecormon at corresponding doses of 9 000, rising to 18 000 units tiw. Non-responders at 8 weeks ceased treatment and responders continued to 20 weeks; at week 12, Epoietin dosing was changed to once weekly at the total responding dose through to week 20. Lenograstim dose was titrated,¹ doubling weekly from 30 µg tiw, to a maximum of 130 µg tiw. Study responses were evaluated by International Working Group criteria.²

Twenty-one patients completed the pharmacodynamic phase of the study and 20 patients proceeded to a therapeutic trial, with a median interval of 3 weeks (range 1-21). Seven patients responded to the therapeutic trial (2 HI-E major, 5 HI-E minor). No responders had an abnormal karyotype. Four out of eight patients with RA with ringed sideroblasts responded. Six responders were by chance within the group of 10 patients who had received bolus of active drugs in the pharmacodynamic phase of study. Incremental change in absolute reticulocyte counts between day 0 and day 7 of the pharmacodynamic study discriminated responders who received bolus EPO/G-

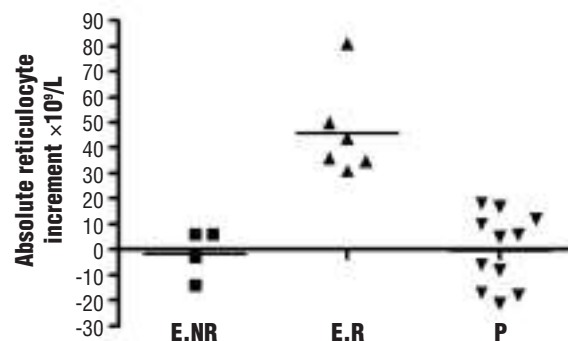


Figure 1. Incremental change in absolute reticulocyte count from day 0 to day 7 of Part 1. E,NR: patients who received a bolus of epoietin+G-CSF in the pharmacodynamic study, and did not respond in the subsequent therapeutic trial; E,R: patients who received a bolus of Epoietin + G-CSF, and responded in the subsequent therapeutic trial; P: patients who received boluses of placebo.

CSF (median increment=40×10⁹/L, range 31-81, n=6), from non-responders who also received bolus EPO/GSCF (median increment = 1.5×10⁹/L, range -14 to 6, n=4) and from patients receiving placebo (median increment=5×10⁹/L, range -21 to 18, n=11) ($p=0.002$, Kruskal Wallis). An increment of >30×10⁹/L was 100% predictive of subsequent response (Figure 1).

In the therapeutic trial, neither Hb, reticulocyte count, nor Transferrin receptor at weeks 1 or 2 predicted for subsequent response. Reticulocyte count (± standard error of the mean) was however non-significantly greater for responders versus non-responders, at both week 1 (189±58×10⁹/L versus 62±16×10⁹/L, $p=0.09$) and week 2 (255±115×10⁹/L versus 69±17×10⁹/L, $p=0.17$). That the reticulocyte count at day 7 was less clearly predictive of response in the therapeutic trial may reflect the different dosing schedule (three time per week) masking a true increase in erythroid output with a continuous reticulocyte shift. Although serum EPO concentrations were both lower in responders than in non-responders this was not significant ($p=0.16$). For responders, hemoglobin concentration at once weekly (qw) Epoietin dosing (weeks 12-20) either did not change compared to tiw dosing (weeks 0-8) ($p>.05$, n=5), or increased in one patient ($p=0.002$). Two patients became iron deficient during weeks 1-8, as measured by serum ferritin <20 µg/L, transferrin saturation <20% and falling CHR. Both patients had baseline serum ferritin <100 µg/L. No iron supplementation was given, and one of these patients (patient 12) still had an erythroid response. No clear evidence for functional iron deficiency was seen on therapy in patients with baseline serum ferritin >100 µg/L.

Thus we have demonstrated in this small phase 2 study that an increment in an easily measured parameter (reticulocyte count) may be predictive of response to recombinant EPO in patients with MDS. Reticulocyte increment at day 7 post bolus injection of epoietin + G-CSF represents the early product of effective erythroid output, and not merely a shift of reticulocytes into the circulation previously observed at an earlier time point in a similarly designed study of MDS patients.³ We have also demonstrated prospectively within the same patients that the once weekly epoietin dosing schedule at the same total weekly epoietin dose is equally efficacious as thrice

weekly dosing. Taken together with the small studies demonstrating erythroid response in MDS patients treated with once weekly dosing,^{4,5} it is reasonable to assume that this should now become the standard dosing schedule. Although we did not use iron supplementation, we found no evidence of functional iron deficiency on treatment in patients with adequate baseline iron stores. Indeed it is of interest that one our best responding responded in an apparently iron-limited environment.

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Errata

The paper *A type II mutation (Glu117stop), induction of allele-specific mRNA degradation and factor XI deficiency* by Solda G, Asselta R, Ghiotto R, Tenchini ML, Castaman G, Duga S (appeared on *Haematologica* 2005; 90:1716-8) was published with a wrong title. Correct version should read as "*Type II mutation (Glu117stop) causes factor XI deficiency by inducing allele-specific mRNA degradation*".