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ORIGINAL REPORT

Intravenous Iron Optimizes the Response to Recombinant Human Erythropoietin in Cancer Patients With Chemotherapy-Related Anemia: A Multicenter, Open-Label, Randomized Trial

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ABSTRACT

Purpose
Recombinant human erythropoietin (rHuEPO) is the standard of care for patients with chemotherapy-related anemia. Intravenous (IV) iron improves hemoglobin (Hb) response and decreases dosage requirements in patients with anemia of kidney disease, but its effect has not been studied in randomized trials in cancer patients.

Methods
This prospective, multicenter, open-label, randomized trial enrolled 157 patients with chemotherapy-related anemia (Hb ≤ 105 g/L, serum ferritin ≤ 450 pmol/L or ≤ 675 pmol/L with transferrin saturation ≤ 19%) receiving subcutaneously rHuEPO 40,000 U once weekly to: (1) no-iron; (2) oral iron 325 mg twice daily; (3) iron dextran repeated 100mg IV bolus; or (4) iron dextran total dose infusion (TDI). Hb and quality of life (QOL) were measured at baseline and throughout.

Results
All groups showed Hb ($P < .0001$) increases from baseline. Mean Hb increases for both IV iron groups were greater ($P < .02$) than for no-iron and oral iron groups. The percentage of patients with hematopoietic responses was higher ($P < .01$) in both IV iron groups (each case 68%) compared with no-iron (25%) and oral iron (36%) groups. IV iron groups showed increases in energy, activity, and overall QOL from baseline, compared with a decrease in energy and activity for no-iron group and no change in activity or overall QOL for oral iron group.

Conclusion
rHuEPO increases Hb levels and improves QOL in patients with chemotherapy-related anemia. Magnitude of Hb increase and QOL improvement is significantly greater if IV iron is added.

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INTRODUCTION

Anemia is now recognized as a significant consequence of cancer and chemotherapy. Chemotherapy-related anemia most closely resembles the anemia of chronic disease, with patients exhibiting serum erythropoietin levels that are elevated above normal but not as high as those demonstrated in patients with similar hemoglobin (Hb) decreases caused by iron-deficiency anemia or hemolytic anemia.[1] It appears that patients with cancer experience a blunted erythropoietin response to anemia,[1] in addition to inadequate erythropoietin production.[2]

Prospective clinical trials have determined that mild-to-moderate anemia occurs in up to 75% of cancer patients undergoing treatment with chemotherapy and/or radiation therapy.[3-5] Data from several large, prospective, multicenter, clinical trials have shown that recombinant human erythropoietin alfa (rHuEPO; PROCRIT; Ortho Biotech Products, Bridgewater, NJ) 10,000 U to 20,000 U or 150 U/kg to 300 U/kg administered three times weekly or 40,000 U to 60,000 U once weekly increases Hb levels,

decreases transfusion requirements, and improves quality of life (QOL) in anemic cancer patients receiving platinum or nonplatinum chemotherapy, independent of tumor response,[6-9] as well as in patients with cancer-related anemia who are not yet receiving chemotherapy.[10] Data also suggest that rHuEPO administration improves health-related QOL and may improve survival in this population.[9,11,12]

Thus, rHuEPO therapy has been established as a mainstay of care for chemotherapy-related anemia.[6-9,13] However, approximately 30% to 50% of cancer patients with chemotherapy-related anemia do not achieve a meaningful response to rHuEPO (a 20-g/L increase in Hb or achieving a Hb level of 120 g/L without transfusion use).[6-9] Further, hematopoietic responses to rHuEPO are not rapid. Many patients do not begin to exhibit an increase in Hb level until after 4 to 6 weeks of rHuEPO therapy.[6-9] Intravenous (IV) (but not oral) iron supplementation has been shown to improve Hb response to rHuEPO, and to decrease rHuEPO dose requirements, in patients with anemia related to chronic kidney disease (CKD).[14-16] Despite these findings, clinicians have been reluctant to prescribe IV iron routinely for cancer patients with chemotherapy-related anemia, primarily because of the risk of anaphylaxis associated with iron dextran.[17] However, this is a relatively rare occurrence. The incidence rate of severe reactions was reported as 0.6% to 0.7% in hemodialysis patients receiving iron dextran.[18] Because the effect of iron and its route of administration have not been studied in randomized trials in the anemic cancer population, the purpose of this study was to evaluate the effect of iron therapy and its optimal route of administration in cancer patients with chemotherapy-related anemia who were concomitantly receiving rHuEPO.

METHODS

Participants

Participants were recruited from the Franklin Square Hospital Center, Baltimore, MD; Carillion Oncology Associates, Roanoke, VA; Washington Hospital Center, Washington, DC; and the New York Harbor Healthcare System, New York, NY. Eligible patients had a histologic diagnosis of cancer, an Hb level $\leq$ 105 g/L, and a serum ferritin concentration of $\leq$ 450 pmol/L, or $\leq$ 675 pmol/L in concert with a transferrin saturation (TSAT) of $\leq$ 19%. Eligible patients were also required to have an Eastern Cooperative Oncology Group performance status $\leq$ 2, a life expectancy of at least 6 weeks, and be scheduled to undergo chemotherapy while on study.

Patients with anemia attributable to factors other than cancer or chemotherapy (ie, B_{12}, or folate deficiency; hemolysis; gastrointestinal bleeding; or myelodysplastic syndromes) were not eligible to participate in the study. Other exclusion criteria included prior transfusion, previous iron dextran therapy, allergy or intolerance to rHuEPO, rHuEPO within 4 weeks of enrollment, uncontrolled hypertension, active infection, prior gastric surgery, and primary bone marrow malignancy or lymphoma metastatic to the bone marrow. Patients with chronic lymphocytic leukemia and multiple myeloma were permitted.

Protocol

This was a prospective, multicenter, open-label, randomized, controlled study. The protocol and informed consent were approved by the Human Studies Committee and the Institutional Review Board at all participating sites. All patients underwent an initial screen within 7 days of enrollment. Baseline information included patient characteristics, tumor site, and current chemotherapy regimen. Baseline laboratory tests included complete blood count, chemical profile, serum iron levels, total iron binding capacity, and serum ferritin level. Participants were then randomly assigned into four treatment groups: (1) no iron, (2) oral iron (ferrous sulfate) 325 mg twice daily, (3) iron dextran 100mg IV bolus at each visit to the calculated dose for iron replacement, and (4) total dose infusion (TDI) of iron dextran. Patients were followed for 6 weeks, except for those in the bolus arm, who were followed until the end of their treatment course. All patients provided written informed consent before study participation.

Patient compliance in group 2 (oral iron) was monitored by weekly telephone interviews. For patients in treatment groups 3 or 4, the total dose of iron dextran was calculated using the following formula to reach a desired Hb level of 140 g/L: dose (mL) = 0.0442 (desired Hb – observed Hb) x LBW + (0.26 $\times$ LBW)[19] where LBW is the patient's lean body weight in kilograms.

Patients randomly assigned to 100mg bolus injections received a 25mg test dose of iron dextran by IV push over 1 to 2 minutes, followed by a 75mg bolus injection, before the first three epoetin alfa doses (ie, for the first 3 weeks of the study). Subsequent iron dextran bolus injections did not require a test dose, provided that the patient did not demonstrate any allergic reaction to the formulation. Participants randomly assigned to TDI received methylprednisolone 125 mg before and following the infusion, which has been shown to ameliorate the arthralgias and myalgias associated with this method of iron dextran administration.[20] Patients then received a 25mg test dose given by IV push. One hour after the test dose was administered, patients received the calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at a rate of 175 mL/h. All patients received iron dextran as INFeD (Watson Pharmaceuticals, Morristown, NJ) except for two patients who received iron dextran as DexFerrum (American Regent Laboratories, Shirley, NY) during a brief period when the first formulation was not available.

All patients received rHuEPO 40,000 U subcutaneously weekly; rHuEPO dose escalation or reduction was not permitted, so not to confound the iron response data.

The primary efficacy variable was defined as the change in Hb from baseline to end point. For patients who completed the study, end point was the maximum Hb level; for all other patients, end point was the Hb level at last observation. Hemoglobin levels were measured at baseline and weekly throughout the treatment period. The secondary efficacy variables included hematopoietic response, time to hematopoietic response, and QOL. Hematopoietic response to rHuEPO was defined as an increase in Hb of $\geq$ 20 g/L or achievement of a Hb level of $\geq$ 120 g/L without transfusion use at any time point during the study. QOL was measured at baseline and weekly during the study using the 100-mm linear analog scale assessment (LASA) of energy level, ability to perform daily activities, and overall QOL. This instrument has been validated in the cancer population,[7] and recent studies have demonstrated a positive correlation between LASA and other validated QOL self-report instruments (ie, Functional Assessment in Cancer Therapy–Anemia subscale).[7] Patients were not aware of their hemoglobin

levels at the time QOL assessments were made or at any other time throughout the study. Treatment-related adverse events were recorded weekly. Arthralgia/myalgia syndrome associated with TDI was graded according to the criteria of Auerbach et al.[21] Oral iron compliance was tracked weekly by investigator query.

Statistical Analysis

The number of patients planned for study enrollment was based on previous data[15] indicating that the interpatient SD for Hb, the primary efficacy variable, was 15 g/L. Assuming a clinically important treatment group difference in mean Hb of 10 g/L, a power of 80%, and a significance level of 0.05, it was determined that 47 patients per group (188 patients total) were required for this study. Patients were centrally randomly assigned.

For quantitative variables, the treatment groups were compared using analysis of variance or the Kruskal-Wallis test, as appropriate. The model used in this analysis allowed treatment group comparisons after adjusting for any center differences. Pairwise comparisons among the treatment groups were based on least squares means, which were also adjusted for any center differences. No adjustment for multiple testing was employed. Within each treatment group the significance of the change from baseline was based on a paired *t*-test. Treatment group comparisons associated with categoric variables were made using Fisher's exact test.

A nonstatistical analysis of possible prognostic indicators included cancer diagnosis (solid tumors *v* hematologic cancers); chemotoxicity (mildly *v* highly myelotoxic chemotherapy, where the latter was defined as chemotherapy for intermediate or high-grade lymphoma or adjuvant chemotherapy for breast cancer); and disease response (stable disease, responsive disease [a 50% decrement in radiographic measurement], progressive disease [measurable worsening of disease], or adjuvant chemotherapy).

For safety data, the intent-to-treat (ITT) population was analyzed. This population was defined as all patients who received at least one dose of study drug. Treatment-related adverse events were documented weekly. Treatment groups were compared with respect to incidence of adverse events using Fisher's exact test.

For all efficacy analyses, a modified ITT population was analyzed. This population was defined as all patients who were randomly assigned and had at least one postbaseline observation. If a patient withdrew before study completion, the last observation before withdrawal was used. In addition, for patients who were transfused or who were given another therapy before study completion, the last observation before that event was used in the analysis. Statistical significance was declared if the two-sided *P* value was $\leq .05$.

RESULTS

Study Population

A total of 157 patients were randomly assigned to receive no-iron (n = 36), oral iron (n = 43), bolus iron dextran (n = 37), or TDI iron dextran (n = 41). Although the study statistical power calculation had required 188 patients to be enrolled, the length of time that the study took precluded some sites from participating so it was decided to close the study before target enrollment was reached. Of the 157 patients randomly assigned, 155 patients had at least one postbaseline Hb value and were included in the modified ITT population. One hundred thirty-two patients completed at least 6 weeks of treatment or all bolus treatments per protocol. Of the 25 patients who did not complete the protocol, 19 received a transfusion, three were administered parenteral iron therapy due to a lack of response to oral or no-iron therapy, one experienced a test dose reaction, and two died (as a result of causes unrelated to the study).

Baseline demographics and clinical characteristics were similar between the four groups ($P \geq .13$; Table 1). The most common cancer diagnoses were lung (27%), gastrointestinal (22%), and breast cancer (18%); 19% of patients were diagnosed with hematologic malignancies (Fig 1). All patients received chemotherapy during the study. There were no significant differences between treatment groups by cancer diagnosis, toxicity of prescribed chemotherapy, or response to chemotherapy.

Patients randomly assigned to the bolus IV iron group received between 11 and 24 doses of 100mg IV iron (total dose range, 1,100 mg to 2,400 mg). Patients randomly assigned to the TDI group received IV iron doses ranging

Table 1. Baseline Clinical Characteristics

Characteristic	No-Iron Group (n = 36)	Oral Iron Group (n = 43)	Bolus Group (n = 37)	TDI Group (n = 41)	*P*
Sex					
Male					
No. of Patients	19	29	18	26	.28
%	53	67	49	63	
Female					
No. of Patients	17	14	19	15	.28
%	47	33	51	37	
Age, years					
Mean	65	66	63	64	.70
SD	11	12	13	11	
Hb, g/L					
Mean	95	97	97	94	.37
SD	9	7	8	10	
LASA, mm					
Energy					
Mean	53	46	42	43	.17
SD	22	23	23	23	
Activity					
Mean	54	51	46	42	.27
SD	26	32	24	24	
Overall QOL					
Mean	57	55	50	49	.47
SD	26	28	25	23	
Ferritin pmol/L					
Mean	294	290	207	240	.13
SD	238	160	153	175	
Transferrin saturation, %					
Mean	15	18	19	14	.28
SD	8	14	17	10	

Abbreviations: TDI, total dose infusion; SD, standard deviation; LASA, Linear Analog Scale Assessment; QOL, quality of life.

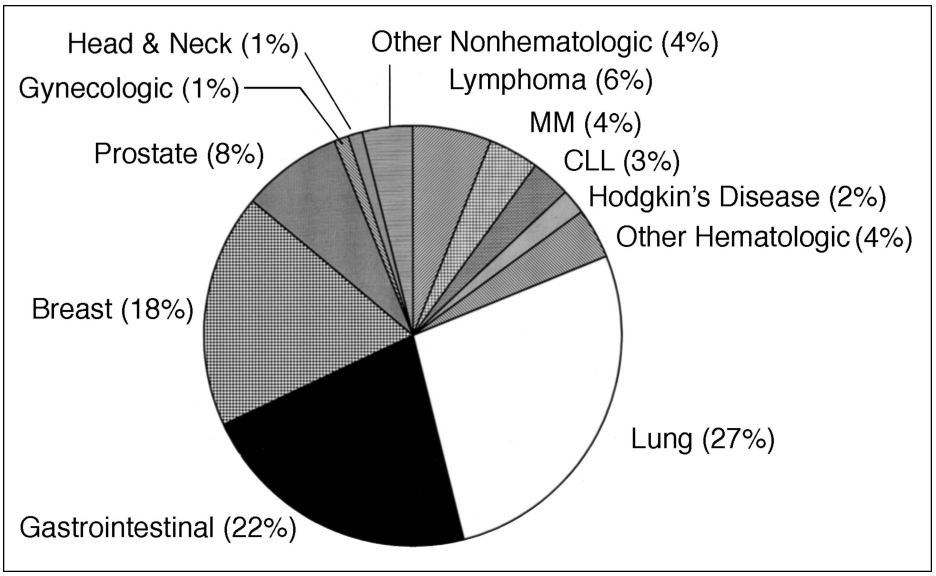

Fig 1. Cancer diagnoses for enrolled patients (n = 157). Solid tumors, 77%; hematologic malignancies, 19%; non-hematologic/other, 4%. CLL, chronic lymphocytic leukemia; MM, multiple myeloma.

from 1,000 mg to 3,000 mg. In the oral iron group, overall compliance exceeded 90%.

Efficacy Evaluations

Hemoglobin response. All treatment groups showed significant ($P < .0001$) increases in Hb level from baseline (Fig 2). Mean increases were 9 g/L, 15 g/L, 25 g/L, and 24 g/L for the no-iron, oral, IV bolus, and TDI groups, respectively. Mean end point Hb levels were 105 g/L, 112 g/L, 122 g/L ($P < .05$ *v* no-iron and oral iron groups), and 119 g/L ($P < .05$ *v* no-iron group), respectively. Mean Hb increases for both IV iron groups were significantly higher than the no-iron and oral iron groups ($P < .02$). There was no significant difference in mean Hb increase between the no-iron and oral iron groups ($P = .21$) or between the two IV iron groups ($P = .53$). Treatment group differences in hemoglobin response seemed to be independent of baseline TSAT (< 15% or > 15%), chemotherapy toxicity (highly myelotoxic or mildly myelotoxic regimens), cancer diagnosis (solid or hematologic cancers), or disease response (progressive disease, stable disease, responsive disease, or adjuvant chemotherapy). In addition, the percentage of patients with a hematopoietic response was significantly higher in the IV iron groups than in the no-iron and oral-iron groups ($P < .01$). Sixty-eight percent of patients in each of the TDI and IV bolus groups achieved a hematopoietic response (at 5.0 ± 1.0 and 9.7 ± 3.3 weeks, respectively) compared with 25% of patients in the no-iron group and 36% of patients in the oral iron group (at 4.2 ± 1.6 and 5.2 ± 0.9 weeks, respectively; Fig 3).

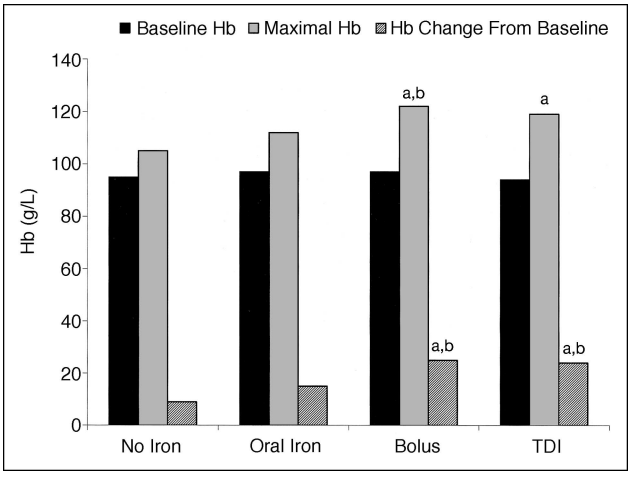

Fig 2. Hb changes from baseline to end point by treatment group for the ITT population. Difference from baseline to end point Hb value, $P < .001$ for all treatment groups. a, $P < .05$ *v* no-iron group; b, $P < .05$ *v* oral iron group.

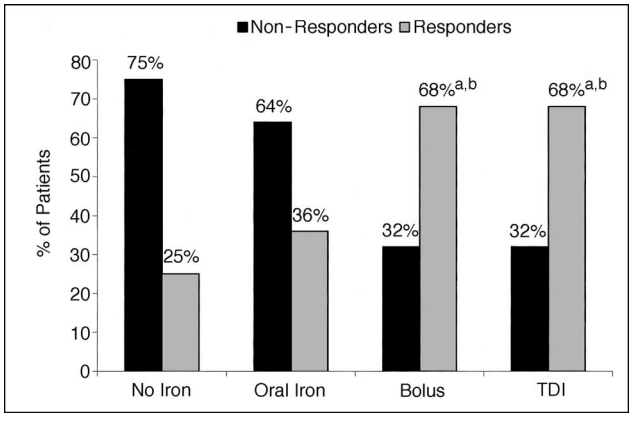

Fig 3. Percentage of responders and nonresponders in each treatment group for the ITT population. Responders were patients who achieved a maximal Hb levels ≥ 120 g/L or an increase in Hb of ≥ 20 g/L during the study. [a] $P < .01$ *v* no-iron group; [b] $P < .01$ *v* oral iron group.

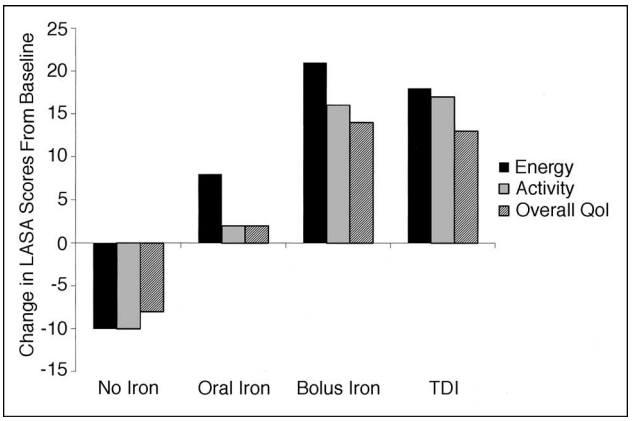

Fig 4. Change in LASA scores from baseline to end point evaluation for the intent-to-treat population. QoI, quality of life; TDI, total dose infustion.

QOL. For energy, activity, and QOL, both IV iron groups showed increases in LASA scores from baseline to end point (Fig 4). For patients who completed the study, end point was defined as the time that maximum Hb was achieved. For all other patients, the end point was defined as the last observation. With the exception of the bolus group end point was no longer than 6 weeks. Conversely, the no-iron group showed small decreases in energy, activity and QOL scores compared with baseline. Although the oral iron group had an increase in energy from baseline, this group had only small changes from baseline in activity or overall QOL. For each of these three parameters, mean increases were observed in the IV iron groups that were greater than those of the no-iron and oral iron groups. When the data for all of the treatment groups were pooled, there was a significant correlation between increase in Hb and improvements in energy ($r = 0.32$, $P < .0001$), activity ($r = 0.30$, $P = .0002$), and overall QOL ($r = 0.31$, $P = .0001$).

Safety. Seven patients experienced adverse events that, in the opinion of the investigator, were related to treatment. Three (7%) of 41 patients in the TDI group experienced an adverse event: delayed arthralgia/myalgia syndrome (two events, grade 1), or acute hypersensitivity reaction (one event). Three (8%) of 37 patients in the bolus group experienced the following adverse events: delayed arthralgia/myalgia syndrome (one event, grade 2), fatigue (one event), or shortness of breath (one event). One (2%) of 43 patients in the oral iron group experienced nausea (one event). The acute hypersensitivity reaction comprised chest/back pain, nausea, vomiting, flushing, and hypotension; it occurred with a test dose (iron dextran as DexFerrum) and precluded further therapy. This event subsequently resolved completely with no residual effects. Two deaths unrelated to study drug were reported; one patient in the oral iron group and one patient in the TDI group died during the study period due to disease progression.

Transfusions and treatment failures. The 22 patients who experienced a clinically significant decrease in Hb level after initiation of therapy were considered treatment failures in the ITT analysis. Nineteen of these patients received transfusions (seven patients in the no-iron group, three patients in the oral iron group, four patients in the IV bolus iron group, and five patients in the TDI iron group; P = not significant). Three patients from no-iron (n = 2) or oral iron (n = 1) groups were given parenteral iron therapy. Two of these patients showed improvements in Hb level (101 g/L to 107 g/L and 100 g/L to 116 g/L). The third patient required a transfusion 2 weeks after parenteral iron therapy was administered. For these 22 patients, study observations before transfusion or alternative therapy were carried forward and used in the ITT analysis.

DISCUSSION

The results of this randomized study demonstrate that rHuEPO increases Hb levels in the absence of iron supplementation or in the presence of oral iron supplementation in cancer patients with chemotherapy-related anemia. In addition, Hb increases were associated with measurable improvements in QOL over the study period, as has been reported in many previous studies.[6-9] Our study is unique in that it further demonstrates that the magnitude of the Hb increase resulting from rHuEPO treatment is significantly greater if IV iron is added to the therapeutic regimen, compared with oral iron supplementation. In addition, a mean Hb increase of more than 20 g/L was achieved after only 6 weeks of rHuEPO plus IV iron therapy in this study whereas, typically, studies have reported this level of Hb increase after 8 weeks or more of rHuEPO treatment. Previous studies have shown that increases in Hb as small as 10g/L are clinically significant.[6,9] The percentage of responders in the IV iron groups (68%) was similar to rates reported in studies using rHuEPO once weekly or three times weekly for 12 weeks or more (49% to 71%).[6-9] Responders were defined as achieving an increase in Hb of ≥ 20 g/L or an Hb level of ≥ 120 g/L, without transfusion use, at any time point during the study. Our results indicate that iron supplementation by the IV route provides the most optimal environment for augmenting erythropoiesis and improving QOL domains. Although methylprednisolone may have a positive effect on QOL variables, the absence of differences between the bolus (no methylprednisolone given) and TDI groups indicates methylprednisolone was not a factor. These findings have important implications for optimizing rHuEPO therapy in the oncology setting and for the cost-effectiveness of this treatment. IV iron represents a new strategy and treatment modality for optimizing the efficacy of rHuEPO in the management of patients with anemia related to cancer and its treatment.

Despite its demonstrated efficacy, approximately 30% to 50% of patients do not exhibit a meaningful response to rHuEPO therapy in clinical trials of 12 to 24 weeks in

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