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The level of reporting of health-related quality of life in cancer research. Evidence from 123 randomised controlled trials enrolling 36220 cancer patients.

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The inclusion of health-related quality of life (HRQOL) in clinical trials presents a number of difficult issues, such as standardization of the procedures for assessment and selection of measurement tools. Recent publications have also raised questions regarding the quality of some published HRQOL assessment studies in cancer clinical trials. We therefore conducted a series of systematic reviews on selected disease sites and pooled these to evaluate the quality of such HRQOL trials.

Systematic reviews were performed, using the Cochrane methodology for six disease sites (colorectal, prostate, non-small cell lung, advanced breast, primary brain and ovarian cancer). Articles were selected from years 1980 to 2002 and were included according to predefined eligibility criteria; e.g. only randomised controlled trials (RCTs) using HRQOL patient self-reported measures. All patients were over 18 and undergoing medical treatment, but this was restricted to systemic therapy for advanced breast cancer. Articles were identified mainly by Medline, Cochrane library, Cancerlit. Each RCT was independently assessed by three reviewers, judged according to a pre-defined set of criteria (e.g. HRQOL baseline data reported, HRQOL measure used, HRQOL missing data reported).

123 trials were identified with 36,220 cancer patients enrolled over the last twenty years. HRQOL was a primary endpoint in 26% of the studies. The measure most often used in these trials was the EORTC QLQ-C30 being used in 40% of the studies. 24% reported who, and/or in which clinical setting the measure was administered. HRQOL baseline compliance data were reported in 69% of the studies and missing data in 57%. 89% used validated HRQOL measures reporting or referencing the related psychometric properties. Timing of HRQOL assessment was reported in 97% of the trials and 86% presented HRQOL results (though sometimes in a very limited way). Overall, the quality of the studies dramatically improved since 1996 reporting more details and comprehensive HRQOL data analysis reflecting greater awareness of the key issues of HRQOL trial methodology.

Over the last two decades a considerable number of trials have contributed to understanding treatment influences in RCTs by providing HRQOL data. Whilst these have clearly helped to plan patient care, a few shortcomings still appear to exist in HRQOL trial design and reporting. Whilst conducting HRQOL studies is far from simple and some organizational issues still challenge researchers in this field, HRQOL data may give a comprehensive picture of the whole treatment benefit.

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Frontloading of darbepoetin alfa improves hemoglobin more rapidly than recombinant human erythropoietin: a combined analysis of data

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Background: Chemotherapy-induced anemia can be treated with erythropoietic therapy (rHuEPO or darbepoetin alfa [Aranesp®]). Standard dosing regimens for these agents stipulate a lower initial dose, which may then be increased at 4-6 weeks for patients with an inadequate response. A dose-finding study of darbepoetin alfa suggested that a higher dose (4.5 mcg/kg weekly [QW]) could increase the proportion of patients who respond to therapy and decrease the average time to response. We therefore hypothesized that a higher initial dose of darbepoetin alfa followed by a lower maintenance dose might provide a more favorable time course of response. This frontloading regimen of darbepoetin alfa was evaluated in several different combinations as described below. The objective of this analysis was to evaluate a frontloading approach for darbepoetin alfa therapy and to compare it to a conventional regimen of rHuEPO by combining data from 3 clinical trials.

Methods: The 3 studies in anemic pts with nonmyeloid tumors had similar enrollment criteria and endpoints. Patients received darbepoetin alfa in one of the following regimens: 4.5 mcg/kg weekly (QW) for 12 wks; frontloading for 4 wks (4.5 mcg/kg QW); frontloading until Hb ≥ 12 g/L (4.5 mcg/kg or 325 mcg QW). The frontloading regimens were followed by a lower dose and/or less frequent schedule of darbepoetin alfa (Q3W in most patients). The comparison group consisted of 115 pts randomized to receive rHuEPO in 2 of these studies. Change in Hb and time to hematopoietic response (HR; 2 g/dL increase in Hb or Hb ≥ 12 g/dL) were calculated adjusting for the effects of RBC transfusion within 28 days. Missing values and values within 28 days of RBC transfusion were imputed by last value carried forward in the intent-to-treat analysis, but were not replaced in the available data analysis.

Results:

	darbepoetin alfa					rHuEPO
	4.5 mcg/kg QW	Frontloading for 4 wk	Frontloading to Hb ≥ 12 g/dL		Total	
			Weight[a]	Fixed[b]		
N	29	60	152	121	362	115
Mean change in Hb (g/dL) after 1 month of therapy: point est (95% CL)						
Intent-to-treat	0.9	0.8	0.8	0.8	0.8	0.5
	(0.5, 1.3)	(0.5, 1.2)	(0.6,1.1)	(0.6, 1.0)	(0.7, 1.0)	(0.2, 0.7)
Available Data	1.0	1.2	1.2	1.2	1.2	0.6
	(0.6,1.4)	(0.8,1.7)	(0.9,1.4)	(0.9, 1.5)	(1.0, 1.3)	(0.3,1.0)
	(n=23)	(n=41)	(n=121)	(n=73)	(n=258)	(n=84)
Kaplan-Meier time to Hematopoietic Response						
Median	6 wk	7 wk	6 wk	6 wk	6 wk	9 wk
(95% CL)	(5, 7)	(6, 12)	(6, 8)	(5,7)	(6,7)	(7,11)

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Optimizing anemia management: flexible epoetin alfa dosing and schedules

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Background: Anemia is a common disease- or treatment-related complication in cancer patients that can affect quality of life (QOL) (Groopman 1999). Epoetin alfa has been shown to increase hemoglobin (Hb) levels, decrease transfusion requirements, and improve QOL in anemic cancer patients (Gabrilove 2001; Littlewood 2001). The greatest incremental improvement in QOL occurs when Hb level increases from 11 to 12 g/dL (range: 11-13 g/dL) (Crawford 2002). Recent studies have examined the clinical benefit of early intervention (mean baseline Hb >10 g/dL) and loading-dose regimens with epoetin alfa to achieve rapid correction and/or maintenance of Hb levels above 12 g/dL.

Methods: Analytic review of data on epoetin alfa dosing regimens was conducted. Data were evaluated for efficacy and safety in cancer patients undergoing chemotherapy.

Results: Three studies enrolling >1,000 breast cancer patients receiving chemotherapy have evaluated efficacy of early intervention with epoetin alfa. In two studies (mean baseline Hb level >12 g/dL), administration of epoetin alfa 40-60,000 IU once weekly maintained Hb at or above mean baseline levels (O'Shaughnessy 2002; Hudis 2002); final mean Hb levels were significantly greater for the epoetin alfa group relative to placebo (P<.001) (O'Shaughnessy 2002) or relative to historic control (P<.05) (Hudis 2002). In a third study (mean baseline Hb 10-12 g/dL), epoetin alfa 10-20,000 IU TIW rapidly increased Hb level to above 12 g/dL and maintained it at this level through study end, with Hb increases of 1 g/dL at 4 weeks and 2.6 g/dL at 8-9 weeks (Pronzato 2002).

Similarly, preliminary results of pilot studies of front-loading regimens in anemic (Hb ≤ 11 g/dL) cancer patients receiving chemotherapy appear promising. Loading regimens of epoetin alfa, 60,000 IU once-weekly initially followed by 40,000 IU once weekly or 120,000 IU every three weeks maintenance, increased mean Hb by >1.0 g/dL at week 4 and by ≥2.5 g/dL at week 8 in two pilot trials (N = 20 for both) (Chap 2002; Patton 2002). Another loading regimen of 5 injections of 40,000 IU epoetin alfa over a period of 2 weeks followed by a 30 day period without treatment increased Hb by 1.7 g/dL and 2.9 g/dL at days 15 and 45, respectively (Cortesi 2002).

Conclusions: Taken together preliminary results show that flexible epoetin alfa dosing strategies can effectively maintain or increase Hb to the optimal level of ≥12 g/dL for maximum improvement in QOL for cancer patients.