Impact of Epoetin-beta on Anemia and Health-related Quality of Life in Cancer Patients: A Prospective Observational Study Using the Generic 15D Instrument

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Abstract. Aim: Cancer-related anemia has a negative impact on the health-related quality of life (HRQoL). Our aim was to evaluate prospectively the effect of treatment of anemia with an erythropoietin on the hemoglobin level and HRQoL in cancer patients with anemia. Patients and Methods: Consecutive patients (N=114) treated for the first time with epoetin (epoetin beta 30000 IU/wk, NeoRecormon®) for anemia during cancer treatment were eligible for study inclusion. Baseline characteristics were collected from patients’ records. HRQoL was measured by the generic 15D instrument and fatigue by visual analogue scale (VAS) at baseline and four months from the start of the treatment with epoetin. The majority (87%) of patients had solid tumors; 69% with a metastatic disease and 89% disease with comorbidities. Results: The mean hemoglobin concentration (SD) in blood increased from 96.6 (8.9) g/L to 112.9 (21.2) g/L, by 16.5 (20.6) g/L (p<0.0001). The mean 15D score rose from 0.72 to 0.77. The change was statistically significant (p=0.0047) and clinically important. The mean fatigue VAS score decreased by 16.0 points, or from 55.4 to 38.4 (+24.4) (p<0.0001). Conclusion: Correction of anemia increased the health-related quality of life in anemic cancer patients, as measured with the generic 15D instrument and the fatigue VAS.

Anemia is a major causative factor in deteriorating the general condition and the health-related quality of life (HRQoL) of patients with cancer, irrespectively of it being due to the underlying disease or its treatment (1-3). It was shown that a mild anemia (Hb <10 g/dL) may become more severe (<9 g/dL) during chemotherapy over quite a short period of time, or even within three weeks, in almost half of the patients (4). Epoetins have been shown to be effective in correcting anemia, in improving quality of life (QoL), and in reducing the need for red blood cell (RBC) transfusions (5-8). Due to concerns regarding the safety of epoetins in terms of an increased risk of thromboembolic complications and even of a potential detrimental effect on survival, epoetins are at present not recommended to patients on radiotherapy or to preventing anemia during chemotherapy (9). However, the evidence connecting the use of epoetins for chemotherapy-induced anemia with poor outcomes, is much less conclusive (10), and the current ESMO guidelines do not recommend against the use of epoetins in patients with a mild (Hb <10 g/dL) chemotherapy-induced anemia (9).

The aim of the present study was to evaluate the effect of treatment of anemia with epoetin-beta on the hemoglobin level and HRQoL in patients with cancer-related anemia.

Patients and Methods

Patients. Anemia patients (N=114) with breast, upper gastrointestinal, colorectal, prostate, lung, bladder or ovarian carcinoma, or multiple myeloma, non-Hodgkin’s lymphoma, chronic lymphocytic lymphoma or any other malignant tumor, where the physician (not connected to the current study) had previously, decided to include epoetin-beta (NeoRecormon®) in treatment management, were recruited to this epidemiological naturalistic prospective study from February, 2006 to November 2010 in four
University Hospitals in Finland. The other main inclusion criteria were a planned non-adjuvant anticancer treatment for at least four months and a life expectancy exceeding six months. The only exclusion criterion was inability to fill-in the HRQoL questionnaires. All patients gave a written informed consent, and the study protocol was approved by the Ethical Committee of Tampere University Hospital (RO5300), authorized by ETENE (The National Advisory Board on Social Welfare and Health Care Ethics).

**Treatment.** The patients were given epoetin-beta (Neo-Recormon®) 30000 IU/week subcutaneously for anemia. The treatment was continued for 16 weeks or until the hemoglobin level reached 120 g/L. The median (range) and mean (SD) number of doses per patient were 13 (0-36) and 12 (6.66), respectively.

**Measurements of health-related quality of life.** HRQoL was measured by the 15D at baseline and four months from the start of the treatment with epoetin beta. The 15D is a generic, 15-dimensional, standardized, self-administered instrument that can be used both as a profile and a single-index score measure. The health state descriptive system (questionnaire) is composed of the following dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. For each dimension, the respondent chooses one of the five levels best describing his/her state of health at the moment (best value=1; worst value=5).

The evaluation system is based on an application of the multi-attribute utility theory. The single-index score (15D score), representing the overall HRQoL on a 0-1 scale (1=full health, 0=being dead) and the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension (value=1) and to being dead (value=0), are calculated from the health state descriptive system by using a set of population-based preference or utility weights. A change of 0.03 in the 15D score is clinically-important in the sense that people can on average feel the difference (11-12). In most of the important properties (reliability, content validity, discriminatory power and responsiveness to change) the 15D compares favorably with other similar type of HRQoL instruments (13-16).

Fatigue was measured separately by a visual analogue scale (VAS) on a 0-100 mm scale (0-10 points) at baseline and four months from the start of the treatment with epoetin beta.

**Study design and statistical analysis.** The present was an epidemiological prospective cohort study, *i.e.* hypothesis-testing observational cohort study, where the one common factor of the patients is cancer-related anemia. To assess the responsiveness of change of 15D, prospective design with two HRQoL measurements was used, in the beginning of anemia, and after treatment approaches. The patients filled the questionnaires twice, at baseline and at four months. The planned sample size was 250 consecutive patients from participating Centers.

In the statistical analysis, a *p*-value less than 0.05 was considered statistically significant. If not stated otherwise, all tests were performed as two-sided and the confidence intervals are two-sided with 95% coverage. The statistical analysis was based on all patients included in the trial. The background information is presented using descriptive statistics. The fatigue VAS’s were analyzed using Analysis of Variance (ANOVA), Visit and Center were included as fixed factors and subject as a random factor in the ANOVA model. The change from baseline to 16 weeks in hemoglobin level was analyzed using an ANOVA model as described above.

**Results**

**Patients.** Patients’ demographic data are presented in Table I. The mean age of patients was 64.9 (range 40-69) years, and two thirds were females. The majority of patients (87%) had solid tumors, out of which ovarian cancer was the most common (N=35), followed by lung (N=20) and prostate cancer (N=11), respectively. Among hematological malignancies (13%), myeloma was the most common diagnosis (N=8). A total of 76 (69%) patients had metastatic disease.

The vast majority of patients was receiving chemotherapy, while 2 patients were receiving radiotherapy. The treatment of 9 patients was marked as “other” without a specification, while information on the therapy for 1 patient is missing. Most patients were either responding (57%) to treatment or having stable disease (26.5%) at baseline (Table II).
Efficacy. During the study period of four months, the mean (SD) concentration of hemoglobin in blood rose from 96.6 (8.9) g/L to 112.9 (21.2) g/L, or by 16.5 (20.6) g/L. The change is statistically highly significant \((p<0.0001)\). The increase in the hemoglobin concentration was at least 10 g/L in 68% of the patients, while in 22% hemoglobin levels remained constant and in 10%, they decreased by at least 10 g/L, respectively. Interestingly, the proportion of patients given transfusions and the number of transfusions per patient remained almost the same throughout the study or 33 (29.5%) and 3.2±2.6 (mean±SD), and 40 (35.4%) and 2.4±1.3, prior to baseline and from baseline until four months, respectively.

Health-related quality of life. The results of the 15D instrument are given in Figure 1. All columns except the one for “mental function” are higher at four months than at baseline, implying a better HRQoL. Accordingly, the mean 15D score rose significantly from 0.72 to 0.77 \((p=0.0047)\) and it is considered to be clinically-important. In individual dimensions, “usual activities” \((p=0.0162)\) and “vitality” \((p<0.0001)\) showed a statistically significant improvement. The positive development in HRQoL took place despite the fact that the number of patients with a progressive disease increased during the study (Table II).

The fatigue VAS score decreased by 16.0 points, or from the value of 55.4±22.1 (mean±SD) to the value 38.4 (±24.4). The difference is highly significant \((p<0.0001)\). The correlations between 15D and the VAS score are given in Figures 2 and 3.

Discussion

This prospective study provides epidemiological data on the use of the novel HRQoL instrument, 15D, in cancer patients with a heavy disease burden. The original goal was to recruit 250 patients, but due to slowing-down of the recruitment rate, the recruitment stopped prematurely. The reason to the
slower-than-expected recruitment was obviously the concerns expressed against the use of epoetins in patients with cancer towards the latter half of 2000’s (17-18). It was decided, however, to analyze the data gathered, rather than abandon them, because it was felt that the novel 15D QoL tool did deserve an evaluation in this setting.

Epoetins have been shown to be effective in correcting chemotherapy-induced anemia in patients with solid tumors (5, 7, 19-20). Also in the present study, the mean hemoglobin concentration in blood increased from 96.6 to 112.9 g/L during treatment with epoetin-beta at a dose of 30000 IU/wk, although transfusions were still needed in approximately one third of the patients after four months of treatment. The need for transfusion is greater than that found in other studies among patients given epoetins (17, 21-22), but less than that in the placebo arm of randomized placebo-controlled trials, where approximately half of patients have needed transfusions (4). An explanation to the rather high demand for transfusions may be that our patient population was quite heavily affected in terms of the extent of disease and general condition; 70% and 90% of the patients had metastasized disease or comorbidities, respectively.

An important finding of the present study is that the QoL of the patients improved during the study despite the fact that in almost half of them, the disease progressed during the four months’ period. The improvement in the global 15D score appeared to result mainly from increased vitality and ability to carry-out usual every-day activities, which belong to key elements in facilitating chances patients have to remain in an ambulatory setting rather than getting hospitalized. Accordingly, also the fatigue VAS score decreased highly significantly during the study period, along with the improvement of the 15D score and the correction of anemia. Our results are on line with previous studies showing an improving quality of life by correcting cancer-related anemia (5-8).

The aim of the present study was not on the safety aspects, therefore detailed data on adverse events are lacking. The investigators were only asked to report treatments for an infection (given to 31.5 % of the patients) or for any “other new condition” (20%). Thus, the numbers of e.g. thromboembolic events and hospitalizations in general are not available.

In conclusion, the increase in the hemoglobin concentration in blood of patients receiving epoetin-beta for cancer-related anemia was reflected in an improvement of QoL, as measured both by the novel HRQoL instrument, or the 15D scale, and the fatigue VAS scale.

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References


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