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# Role of Cresp® in the management of chemotherapy-induced anemia in cancer patients: A real-world clinical practice audit

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## Abstract

**Introduction:** Anemia is a common, underestimated problem in cancer patients receiving myelosuppressive chemotherapy and has significant adverse effect on the quality of life and outcome. Darbepoetin has been shown to be effective in this setting, but controversy surrounds it actual use. **Methods:** We analyzed prospectively collected clinical practice data of patients receiving darbepoetin in a real-world setting for this retrospective audit. Patients with baseline hemoglobin (Hb) of <11 g/dl were included in this analysis. Their medical records were audited using a predetermined 35-point pro forma. **Results:** There were a total of 274 patients with advanced cancer receiving myelosuppressive chemotherapy who had baseline Hb <11 g/dl and who were given darbepoetin. Head-and-neck squamous cell carcinoma, lung cancer, and breast cancer were the most common cancers. Their median baseline Hb was 8.9 g/dl which rose to 11.2 g/dl at the end of commenced therapy, along with improved symptomatology. There were no new toxicities, and only two patients required discontinuation of darbepoetin due to toxicity. **Conclusion:** Darbepoetin is safe and effective in the prevention and management of anemia among patients receiving myelosuppressive chemotherapy.

**Key words:** Hemoglobin, India, prophylaxis, quality of life, supportive care

## Introduction

The European Cancer Anaemia Survey study involving 24 countries reported that 83% of cancer patients receiving chemotherapy develop anemia during their course of illness.[1,2] Such patients with anemia also have fatigue, weakness, breathlessness, poor performance status, and worse quality of life (QoL).[3,4] Anemia in cancer patients has also been associated with higher mortality and poorer prognosis.[5] One important factor is due to underreporting of chemotherapy-induced anemia (CIA) – with more than half of them not receiving anemia directed therapy during treatment of their cancer.

Alkylating agents and platinum-based chemotherapy have double the risk of anemia.[1,6] Low baseline hemoglobin (Hb) (≤12.9 g/dL in females and ≤13.4 dL in males) and concurrent treatment with chemotherapy/radiation therapy are also risk factors of CIA.[1] Patients with lung cancer or gynecologic cancer also have higher risk for anemia, being 39% for single-modality treatment (either chemotherapy or radiation therapy) and 50% for concomitant chemoradiotherapy (50%).[3]

Among cancer patients receiving chemotherapy and developing anemia (Hb ≤11 g/dL), 63% are shown to document moderate-to-severe fatigue.[7] Other features commonly seen in CIA, such as insomnia, anorexia, depression peripheral edema, sustained tachycardia, chest pain, and exertional dyspnea, also impair QoL substantially.[7-9] Fortunately, these symptoms have been shown to improve along with rise in Hb levels.[10]

While the treatment options for CIA include erythropoiesis-stimulating agents (ESAs), iron supplementation, or transfusion, our focus in this study is to document the use of darbepoetin biosimilar (Cresp®) in a real-world clinical practice setting.[11-14]

## Methods

This is an audit of prospectively documented data of patients with advanced cancer receiving chemotherapy and whose baseline Hb was <11 g/dl. Those who also received darbepoetin in a real-world setting (2.25 µg/kg/week given three weekly) were included in this analysis.[15,16] Their medical records were scrutinized till the end of chemotherapy and 35 parameters were analyzed. Status of cancer [Table 1] at baseline and last follow-up (FU), adherence to chemotherapy and Cresp scheduling, predetermined clinical features, Hb level, and requirement of red blood cell (RBC) transfusions [Table 2], as well as toxicities [Table 3], were the focus of this evaluation.

## Results

Data from 274 patients (159 males and 115 females) fulfilled the requirement for audit. The median age of these patients was 47 years (range: 21–86 years).

All patients were in advanced stage of the disease (Stage III or IV), requiring potentially myelosuppressive chemotherapy as part of their standard of care treatment.

All patients received potentially myelosuppressive combination chemotherapy (two- or three-drug combination protocols) for six to eight cycles. Nearly 39% of patients received

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**Table 1: Site of primary tumor (type of cancer)**

| Serial number | Primary site | Males (*n*) | Females (*n*) | Total, *n* (%) |
|---|---|---|---|---|
| 1 | Head-and-neck SCC | 81 | 28 | 109 (39.78) |
| 2 | Lung cancer | 49 | 15 | 64 (23.35) |
| 3 | Breast cancer | 0 | 51 | 51 (18.61) |
| 4 | Colorectal cancer | 17 | 1 | 18 (6.57) |
| 5 | Ovarian cancer | 0 | 17 | 17 (6.20) |
| 6 | Esophageal cancer | 3 | 1 | 4 (1.46) |
| 7 | Others | 9 | 2 | 11 (4.01) |
| Total | | 159 | 115 | 274 |

SCC=Squamous cell carcinoma

**Table 2: Clinical features at baseline and end of chemotherapy**

| Clinical features | Baseline (*n*=274), *n* (%) | End of chemotherapy (*n*=233), *n* (%) |
|---|---|---|
| Fatigue | 101 (36.86) | 34 (14.59) |
| Dyspnea | 37 (13.50) | 12 (5.15) |
| Weakness | 149 (54.38) | 46 (19.74) |
| Headache | 52 (18.98) | 11 (4.72) |
| Fever | 23 (8.39) | 3 (1.29) |
| Myalgia | 155 (56.57) | 28 (12.02) |
| Nausea | 21 (7.66) | 32 (13.73) |
| Diarrhea | 5 (1.82) | 17 (7.30) |
| Chest pain | 9 (3.28) | 21 (9.01) |
| Median Hb (g/dl) | 8.9 | 11.2 |
| Patients requiring RBC transfusion(s) | NA | 8 (3.43) |

Hb=Hemoglobin, RBC=Red blood cell, NA=Not available

**Table 3: Side effects during darbepoetin (Cresp®) therapy**

| Toxicity | Incidence, *n* (%) |
|---|---|
| Cardiac arrhythmia | 4 (1.46) |
| CCF | 8 (2.92) |
| Hypertension | 52 (18.98) |
| Hypotension | 2 (0.73) |
| Infection | 24 (8.76) |
| Sepsis | 3 (1.10) |
| Thrombosis | 4 (1.46) |
| Vascular access thrombosis | 7 (2.56) |
| Discontinuation/delay of CT due to toxicity | 34 (12.41) |
| Discontinuation/delay of darbepoetin due to toxicity | 2 (0.73) |

CT=Commenced therapy, CCF=Congestive cardiac failure

platinum-based combination chemotherapy. Drugs used included gemcitabine, pemetrexed, 5-fluorouracil, docetaxel, paclitaxel, oxaliplatin, capecitabine, adriamycin, carboplatin, cisplatin, And darbepoetin (Cresp, Dr. Reddy's Laboratories, Hyderabad, Telengana, India) which were administered 500 µg subcutaneously for every three weeks.

Of the 274 patients who commenced therapy (CT), 233 were able to complete the intended CT (29 had Progressive Disease (PD), 5 due to toxicity, and 7 either died or were lost to FU). Of the 233 patients who were evaluated at the end of CT, 61 (26.18%) achieved complete response, 107 (45.92%) partial response, and 65 (27.90%) stable disease.

Three-weekly Cresp doses were given for a median of four times (range: 1–8 times). The major reason for missing or discontinuing Cresp was due to patient's wish (financial reasons). Cresp was discontinued due to toxicity only in two cases. The median baseline Hb was 8.9 g/dl (range: 6–10 g/dl). The last documented Hb was a median of 11.2 g/dl (range: 9.41–14.6 g/dl). Eight patients required RBC transfusion and were considered as failure of Cresp.

## Discussion

Erythropoietin (EPO) is produced endogenously in humans and is responsible for regulating maturation, proliferation, and differentiation of RBCs.[17] Chemotherapy myelosuppression reduces the endogenous production of EPO, leading to anemia. Thus, the use of pharmacological doses of ESA treatments is aimed at overcoming the effect of chemotherapy-induced myelosuppression in the EPO-deficient setting.

Cancer patients on chemotherapy need support when their Hb concentration falls below 10 g/dL.[18] Darbepoetin alfa (as compared to conventional EPO) needs to be administered less frequently – having a longer half-life with improved biologic activity.[12,15] Close monitoring of patients receiving darbepoetin is mandatory for efficacy, toxicity, and dose modification as per guidelines, and the US Food and Drug Administration even issued a black box warning.[19] However, the experience on either side of the Atlantic ocean has been a lesson in contrast. While the USA floundered and faced significant toxicity, Europe was able to continue using EPO without safety issues. The fundamental difference was in the adherence to the guidelines in Europe – with careful attention to all recommendations – in which patients should consider EPO, Hb level at which to start EPO, dose of EPO to be given, frequency of monitoring, criteria for dose adjustments, as well as level of Hb at which to discontinue further EPO.

These are the largest data on the use of Cresp (darbepoetin biosimilar) in cancer patients. They reflect its use in a multitude of common solid tumors including head-and-neck, lung, and breast cancers. Administration of long-acting Cresp allowed seamless integration into the patients' chemotherapy schedule, without increasing the need to visit health-care professionals/hospitals. The median increase in the Hb level from baseline was 2.3 g/dl, indicating a very good response. Eight patients required RBC transfusions and two other patients required discontinuation of Cresp due to toxicity. This gives an overall failure rate of only 4.29% (10/233).[20-22] Anemia-related symptoms also showed improvement in the majority of patients. Toxicity was in line with published literature, and there were no unexpected or new safety concerns.

Initial fear that darbepoetin is associated with higher (22%) cardiovascular and/or thromboembolic adverse events as compared to placebo (15%) has not been proven to be appropriate in subsequent randomized controlled trials.[23] Hence, the fear of adverse impact on overall survival has also been shown to be incorrect by several recent publications.[24-28]

Thus, the correct use of ESAs to treat anemia in cancer patients receiving myelosuppressive chemotherapy is appropriate, safe, and beneficial.[29] In order to maximize the benefit for patients, it is recommended to follow published guidelines in general.[30,31] For individual patients, management may also be necessary to personalize information on energy conservation methods, diet modification, and graded exercise scheduling – aspects entirely under the control of the patient/family, and following related doctors instructions are vital to optimise treatment benefit. Doing so has also been shown to provide cost-effective management of patients.[32]

In summary, the take-home messages are shown in Table 4.

**Table 4: Take-home messages**

| Serial number | Key Message |
|---|---|
| 1 | These are the largest data ($n$=274) on the use of Cresp (biosimilar darbepoetin) in advanced cancer patients receiving potentially myelosuppressive chemotherapy |
| 2 | It includes all common solid tumors including head-and-neck, lung, and breast cancers |
| 3 | Of the 233 patients who were evaluated at the end of CT, 61 (26.18%) achieved CR, 107 (45.92%) PR, and 65 (27.90%) SD |
| 4 | Cresp was administered at a dose of 500 µg SC thrice weekly and patients received the injection at a median of four times (range: 1-8 times) |
| 5 | Median increase in the Hb level was 2.3 g/dl (baseline Hb was 8.9 g/dl [range 6-10 g/dl] and post-CT, increase in Hb level was a median of 11.2 g/dl [range 9.41-14.6 g/dl]) |
| 6 | There was symptomatic improvement in all patients with respect to anemia-related symptoms |
| 7 | Eight patients required RBC transfusions and two other patients required discontinuation of Cresp due to toxicity. This gives an overall failure rate of only 4.29% (10/233) |

CT=Commenced therapy, Hb=Hemoglobin, RBC=Red blood cell, PR=Partial response, SD=Stable disease, CR=Complete response

## Conclusion

Darbepoietin is safe and effective in the prevention and management of anemia among patients receiveing myelosuppressive chemotherapy. Cresp should be considered in all solid tumor patients with high risk of chemotherapy induced anemia as well as those who develop the anemia while on chemotherapy.

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### Conflicts of interest

There are no conflicts of interest.

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