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

Ghanshyam Biswas, Avinash Pandey[1], Nikhil Ghadyalpatil[2], Nilesh Lokeshwar[3], Boben Thomas[4], Anita Ramesh[5], Yogesh Arora[6], Chandragouda Dodagoudar[7], Vibha Naik[8], Ashish Joshi[9], Indranil Ghosh[10], Rakesh Roy[11], Medhi Kunjahari[12], Tejinder Singh[13], Palanki Dattatreya Satya[14], Sachin Hingmire[15], Purvish M Parikh[16]

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

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/sajc.sajc_246_19

Department of Medical Oncology, Sum Hospital, Bhubaneswar, Odisha, [1]Department of Medical Oncology, RCC, Patna, Bihar, [2]Department of Medical Oncology, Yashoda Hospital, Secunderabad, [14]Department of Medical Oncology, Omega Hospital, Hyderabad, Telangana, [3]Department of Medical Oncology, Asian Cancer Institute, [9]Department of Medical Oncology, Mumbai Oncocare Center, [13]Department of Medical Oncology, Fortis Hospital, Mumbai, [15]Department of Medical Oncology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, [4]Department of Medical Oncology, Kerala Institute of Medical Sciences, Trivandrum, Kerala, [5]Department of Medical Oncology, Apollo Specialty Hospital, Chennai, Tamil Nadu, [6]Department of Medical Oncology, Mohandai Oswal Hospital, Ludhiana, Punjab, [7]Department of Medical Oncology, BLK Superspeciality Hospital, [12]Department of Medical Oncology, Batra Cancer Center, Delhi, NCR, [8]Department of Medical Oncology, Naik Hospital, Baroda, [16]Department of Medical Oncology, Shalby Cancer and Research Institute, Ahmedabad, Gujarat, [10]Department of Medical Oncology, Apollo Hospital, [11]Department of Pain and Palliative Care, Saroj Gupta Cancer Hospital, Kolkata, West Bengal, India
Correspondence to: Prof. Purvish M Parikh,
E-mail: purvish1@gmail.com

How to cite this article: Biswas G, Pandey A, Ghadyalpatil N, Lokeshwar N, Thomas B, Ramesh A, *et al*. Role of Cresp® in the management of chemotherapy-induced anemia in cancer patients: A real-world clinical practice audit. South Asian J Cancer 2020;9:59-61.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Barrett-Lee PJ, Ludwig H, Birgegård G, Bokemeyer C, Gascón P, Kosmidis PA, *et al.* Independent risk factors for anemia in cancer patients receiving chemotherapy: Results from the European Cancer Anaemia Survey. Oncology 2006;70:34-48.
2. Pirker R, Pirolli M, Quigley J, Hulnick S, Legg J, Collins H, *et al.* Hemoglobin decline in cancer patients receiving chemotherapy without an erythropoiesis-stimulating agent. Support Care Cancer 2013;21:987-92.
3. Kosmidis P, Krzakowski M. ECAS Investigators. Anemia profiles in patients with lung cancer: What have we learned from the European cancer anaemia survey (ECAS)? Lung Cancer 2005;50:401-12.
4. Platzbecker U, Hofbauer LC, Ehninger G, Hölig K. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes. Leuk Res 2012;36:525-36.
5. Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist 2008;13 Suppl 3:33-6.
6. Yarbro CH, Frogge MH, Goodman M. editors. Cancer Nursing: Principles and Practice 6th ed. Sudbury, MA: Jones and Bartlett; 2005.
7. Gabrilove JL, Perez EA, Tomita DK, Rossi G, Cleeland CS. Assessing symptom burden using the M. D. Anderson symptom inventory in patients with chemotherapy-induced anemia: Results of a multicenter, open-label study (SURPASS) of patients treated with darbepoetin-alpha at a dose of 200 microg every 2 weeks. Cancer 2007;110:1629-40.
8. van Weert E, Hoekstra-Weebers J, Otter R, Postema K, Sanderman R, van der Schans C, *et al.* Cancer-related fatigue: Predictors and effects of rehabilitation. Oncologist 2006;11:184-96.
9. National Comprehensive Cancer Network. Cancer-and Chemotherapy-Induced Anemia. Available from: http//www.nccn.org. [Last retrieved on 2009 Mar 21].
10. National Comprehensive Cancer Network. Cancer-Related Fatigue. Available from: http://www.nccn.org. [Last retrieved on 2009 Mar 21].
11. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, *et al.* Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol 2008;26:132-49.
12. Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, *et al.* Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006;98:273-84.
13. Bastit L, Vandebroek A, Altintas S, Gaede B, Pintér T, Suto TS, *et al.* Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-8.
14. Steinmetz T, Schröder J, Plath M, Link H, Vogt M, Frank M, *et al.* Antianemic treatment of cancer patients in German routine practice: Data from a prospective cohort study-the tumor anemia registry. Anemia 2016;2016:8057650.
15. Available from: https://www.cresp.in/pdf/PI.pdf. [Last accessed on 2017 Dec 17].
16. Available from: http://www.drreddys.com/media/press-releases/aug9_2010.html. [Last accessed on 2017 Dec 17].
17. Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, *et al.* Cancer-related anemia: Pathogenesis, prevalence and treatment. Oncology 2005;68 Suppl 1:3-11.
18. Charu V, Saidman B, Ben-Jacob A, Justice GR, Maniam AS, Tomita D, *et al.* A randomized, open-label, multicenter trial of immediate versus delayed intervention with darbepoetin alfa for chemotherapy-induced anemia. Oncologist 2007;12:1253-63.
19. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, *et al.* American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol 2010;28:4996-5010.
20. Smith SW, Sato M, Gore SD, Baer MR, Ke X, McNally D, *et al.* Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes. Haematologica 2012;97:15-20.
21. Harnan S, Ren S, Gomersall T, Everson-Hock ES, Sutton A, Dhanasiri S, *et al.* Association between transfusion status and overall survival in patients with myelodysplastic syndromes: A systematic literature review and meta-analysis. Acta Haematol 2016;136:23-42.
22. Revicki DA, Stull D, Vernon M, Rader M, Tomita D, Viswanathan HN, *et al.* Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in four randomized, placebo-controlled clinical trials. Qual Life Res 2012;21:311-21.
23. Gordon D, Nichols G, Ben-Jacob A, Tomita D, Lillie T, Miller C, *et al.* Treating anemia of cancer with every-4-week darbepoetin alfa: Final efficacy and safety results from a phase II, randomized, double-blind, placebo-controlled study. Oncologist 2008;13:715-24.
24. Zachariah M, Elshinawy M, Alrawas A, Bashir W, Elbeshlawi I, Tony S, *et al.* Single dose darbepoetin alfa is useful in reducing red cell transfusions in leukemic children receiving chemotherapy. Pediatr Hematol Oncol 2014;31:442-7.
25. Vansteenkiste J, Wauters I, Elliott S, Glaspy J, Hedenus M. Chemotherapy-induced anemia: The story of darbepoetin alfa. Curr Med Res Opin 2013;29:325-37.
26. Vansteenkiste J, Glaspy J, Henry D, Ludwig H, Pirker R, Tomita D, *et al.* Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: Study-level and patient-level meta-analyses. Lung Cancer 2012;76:478-85.
27. Nitz U, Gluz O, Zuna I, Oberhoff C, Reimer T, Schumacher C, *et al.* Final results from the prospective phase III WSG-ARA trial: Impact of adjuvant darbepoetin alfa on event-free survival in early breast cancer. Ann Oncol 2014;25:75-80.
28. Ohashi Y, Uemura Y, Fujisaka Y, Sugiyama T, Ohmatsu H, Katsumata N, *et al.* Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-controlled trials. Cancer Sci 2013;104:481-5.
29. Bohlius J, Tonia T, Nüesch E, Jüni P, Fey MF, Egger M, *et al.* Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: Systematic review and meta-analyses of published and unpublished data. Br J Cancer 2014;111:33-45.
30. Van Belle S, Swieboda-Sadlej A, Karanikiotis C, Labourey JL, Galid A, Wheeler T, *et al.* A final analysis from the CHOICE study examining darbepoetin alfa use for chemotherapy-induced Anaemia in current European clinical practice. Curr Med Res Opin 2012;28:1079-87.
31. Motola D, Vaccheri A, Roncadori A, Donati M, Bonaldo G, Covezzoli A, *et al.* Comparative risk/benefit profile of biosimilar and originator erythropoiesis-stimulating agents (ESAs): Data from an Italian observational study in nephrology. Eur J Clin Pharmacol 2018;74:805-10.
32. Duran A, Spaepen E, Lamotte M, Walter E, Umuhire D, Lucioni C, *et al.* Cost analysis: Treatment of chemotherapy-induced anemia with erythropoiesis-stimulating agents in five European countries. J Med Econ 2012;15:409-18.