Utilisation review of epoetin alfa in cancer patients at a cancer centre in Singapore

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ABSTRACT

Introduction: Recombinant erythropoietin-stimulating agents have been used to ameliorate the symptoms of anaemia in cancer patients. However, there have been concerns about an increased risk of thromboembolic events and mortality. This study reviews the usage of epoetin alfa in treating chemotherapy-induced anaemia at the National Cancer Centre Singapore (NCCS), as well as the prescribing and monitoring practices employed.

Methods: Cancer patients who have received at least one dose of epoetin alfa at the NCCS between January 1, 2005 and October 15, 2007 were included in this study.

Results: A total of 121 patients were identified and 91 patients were eligible for data collection. The majority of patients manifested breast cancer (30.8 percent) and ovarian cancer (15.4 percent). Over 90 percent of the patients were receiving either chemotherapy or radiotherapy when epoetin alfa was initiated. Epoetin alfa was initiated at a median haemoglobin level of 8.7 (range 7–14.3) g/dL. Approximately 41.8 percent of the patients had a positive response after the initiation of epoetin alfa. Baseline iron studies were performed in 12.1 percent of the patients. Blood pressure was uncontrolled, according to the Singapore Ministry of Health Hypertension guideline, in a substantial number of patients (32.6 percent) prior to the initiation epoetin alfa. There were no documented thromboembolic events.

Conclusion: This study identified a broad range of practices in the utilisation of epoetin alfa at NCCS, which may explain the variable patient response to epoetin alfa. The results of this study will be used to improve the management of chemotherapy-induced anaemia at the institution.

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INTRODUCTION

Anaemia is a common complication of chemotherapy. Chemotherapy-induced anaemia is commonly observed in the treatment of solid tumours, particularly in the treatment of lung cancers and genitourinary cancers.[1] This is due to the direct myelosuppressive effects of chemotherapy on the bone marrow, as the production of red blood cells may be compromised due to chemotherapy-induced damage of the erythropoietin-producing renal tubules. Treatment options for chemotherapy-induced anaemia include blood transfusions, iron supplementation and recombinant erythropoietin stimulating agents (ESAs).[2,3] Blood transfusions can provide immediate symptomatic relief to anaemia. However, blood transfusions are also limited by the potential risks of fluid overload and infections. Besides, transfusions can also take a significant amount of time to obtain and administer.

Erythropoiesis, which is the formation of red blood cells in the bone marrow, is stimulated by erythropoietin that appears when peripheral tissues, especially the kidney tissues, are exposed to low oxygen conditions.[4] ESAs mimic the action of erythropoietin as they stimulate erythropoiesis by interacting with specific erythropoietin receptors on red blood cell progenitors. This leads to proliferation and differentiation along the reticulocyte pathway, resulting in the correction of anaemia.[5] Several large scale clinical trials have demonstrated the benefits of ESAs, such as increasing haemoglobin levels, reducing the need for red blood cell transfusions, providing symptomatic relief and improving the quality of life for patients with chemotherapy-induced anaemia.[6,7]

Over the past few years, safety concerns over ESAs have received much publicity globally. In 2003, two randomised trials demonstrated a significant decrease in the survival rate of cancer patients who received ESAs. Subsequently, the Pharmacovigilance Advisory Committee (PVAC) of the Health Sciences Authority

released cautionary warnings stating that ESAs can increase tumour promotion or decrease survival with excessive target haemoglobin above 12 g/dL. The PVAC recommended that: (1) ESAs should not be used for the prevention of anaemia in cancer patients, and (2) target haemoglobin concentrations in cancer patients, if treated with ESAs, should be up to 12 g/dL.[8] Similar warnings were endorsed by the United States Food and Drug Administration (FDA) Oncology Drugs Advisory Committee (ODAC), and these events led FDA to revise the approved product labels for the ESAs – incorporating the black box warning, the most severe type of warning, against the off-label use of ESAs.[9-11] To date, a total of ten controlled trials have demonstrated that ESAs may lead to a worse outcome – either by an increase in mortality or tumour progression.[11-20] In these trials, ESAs were used according to the on-label recommendations and administered (1) at higher doses; (2) to target a haemoglobin level higher than the indicated level of 12 g/dL; or (3) to patients who were not concurrently on chemotherapy treatment. Incorporating data from these clinical trials, a recently published meta-analysis proclaimed that the utilisation of ESAs in cancer patients is associated with an increased risk of thromboembolic events (relative risk 1.57; 95% confidence interval [CI] 1.31–1.87) and an increased mortality risk (hazard ratio 1.10; 95% CI, 1.01–1.20).[21]

It is important to note that off-labelled usage of ESAs is the primary suspicion for why ESAs have contributed to the increased number of cardiac and mortality events. Nonetheless, the ODAC committee continues to support the use of ESAs as of March 2008, based on the relative risks and benefits presented. With regard to the safe usage of ESAs, multiple organisations have recently updated their recommendations. For instance, the American Society of Hematology and American Society of Clinical Oncology have released a joint update on their clinical practice guidelines on the use of epoetin alfa and darbepoetin in September 2007.[2] New recommendations acknowledge the elevated risk of thrombotic complications due to ESAs, and advise clinicians to use these agents judiciously and not deviate from the on-label usage.

In lieu of the recent safety concerns of ESAs, we performed a retrospective drug utilisation review to report the usage of ESAs, particularly epoetin alfa, at a cancer centre in Singapore. Besides assessing the response to epoetin alfa in our local cancer patients, this retrospective analysis can provide insight into the prescribing practices of epoetin alfa in our local setting, aiming to improve clinicians' prescribing habits for epoetin alfa.

METHODS

This is a retrospective, single centre, drug utilisation study of epoetin alfa in a cancer centre. Approval was received from the Institutional Review Board. All investigators completed the Good Clinical Practice and Biomedical Research Investigators and Key Personnel online courses initiated by the Collaborative Institutional Training Initiative. Patients who had haematological and non-haematological malignancies treated with chemotherapy, and who received at least one dose of epoetin alfa at the National Cancer Centre Singapore (NCCS) between January 1, 2005 and October 15, 2007, were included in this study. Patients were identified from an electronic chemotherapy prescription database and medication profiles were reviewed. In order for a patient to be included in this study for evaluation, complete information including chemotherapy treatments as well as details of epoetin alfa therapy such as dosing, dosing frequency and monitoring parameters must have been fully available.

The target haemoglobin level of epoetin alfa treatment was set to be 11–12 g/dL, in reference to the National Comprehensive Cancer Network guidelines for the optimal haemoglobin level for anaemic cancer patients treated on erythropoietin-stimulating agents. To determine whether a patient was receiving an appropriate dose of epoetin alfa and whether a dose adjustment was needed, the following definitions were employed in this study. An "excessive" response was defined as a rise in the haemoglobin level of more than 1 g/dL within two weeks of ESAs treatment or when haemoglobin levels exceeded 12 g/dL. A "poor" response was defined as an increase in the haemoglobin level of less than 0.5 g/dL after 2–6 weeks of treatment. Otherwise, if a patient could continue on the same prescribed dose of ESA, the response was labelled as "positive".

Patients were defined to manifest "uncontrolled hypertension" if their blood pressure assessments at the initiation of epoetin alfa exceeded the defined blood pressure goal. In keeping with the Singapore Ministry of Health hypertension guidelines, the blood pressure goal of normal hypertensive patients without cardiac risk factors was 140/90 mmHg, while that for hypertensive patients with diabetes mellitus or chronic renal disease was 130/80 mmHg.[22] The documentation of blood pressure by NCCS staff was tracked from both clinic and nursing case notes. All data analyses were performed using Microsoft Excel® and the Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were summarised in frequencies and percentages. One-way ANOVA test was utilised to evaluate whether demographic

factors contributed to the individual responses of epoetin alfa. A two-sided $p < 0.05$ was considered to be statistically significant.

RESULTS

121 cancer patients were prescribed epoetin alfa between January 1, 2005 and October 15, 2007. However, only 91 patients had complete information for evaluation. The majority of the patients (67.1%) manifested cardiovascular comorbidities, such as ischaemic heart disease, hypertension and hyperlipidaemia. Three patients (3.3%) were diagnosed with anaemia prior to chemotherapy, and one patient (1.1%) had a history of ischaemic stroke (Table I). Private patients and non-residents formed the main bulk of patients using epoetin alfa (70.4%). A large proportion of the patients (40.7%) were prescribed epoetin alfa at 40,000 U once weekly. Other common dosing regimens included 40,000 U given as one single dose (29.7%), 40,000 U administered twice monthly (5.5%) and 10,000 U once every ten days (8.8%). The median haemoglobin level at which epoetin alfa therapy was initiated was 8.7 (range 7–14.3) g/dL. Over 80% of epoetin alfa therapy was initiated between haemoglobin levels of 7 and 10 g/dL (Table II). Among all the patients who received epoetin alfa, 29 (31.9%) received blood transfusions either before or after epoetin alfa was initiated, 11 patients received fewer episodes of blood transfusion after epoetin alfa was started, while five patients received the same number of blood transfusions and 13 received more blood transfusions after epoetin alfa was started.

Complete blood counts were assessed at least every two weeks for 70 patients (76.9%) who were started on epoetin alfa. Regarding the haemoglobin response to epoetin alfa within 2–6 weeks of initiation, 38 patients (41.8%) had a "positive" response to epoetin alfa, whereas 25 patients (27.5%) and 28 patients (30.8%) had an "excessive" and "poor" response to epoetin alfa, respectively. Among patients who were classified as "poor" responders to epoetin alfa, only two received a dosage adjustment for their erythropoietin therapy. With regard to the patients who had an "excessive" response to epoetin alfa, only eight patients (32%) had their epoetin alfa therapy withheld or discontinued. None of these patients received a dosage reduction according to the package insert recommendations. Overall, only 31 patients (34.1%) had reached a target haemoglobin level of 11–12 g/dL before the medication was discontinued. None of the patients' demographics, including age, ethnicity, gender, the prescribing of iron supplementation, cancer diagnosis and the presence of metastatic disease, predicted the response to epoetin alfa therapy ($p > 0.05$).

Table I. Patient demographics.

Patient demographics	No. (%) of patients (n = 91)
Gender	
Male	29 (31.9)
Female	62 (68.1)
Ethnicity	
Chinese	62 (73.6)
Malays	4 (4.4)
Indians	7 (7.7)
Others	18 (14.3)
Median (range) weight (kg)	55 (40–72)
Median (range) age (years)	62 (16–88)
Cancer diagnosis	
Breast cancer	29 (31.9)
Ovarian cancer	14 (15.4)
Lung cancer	8 (8.8)
Gastrointestinal cancer	18 (19.8)
Genitourinary cancer	5 (5.5)
Others	17 (18.7)
Metastatic disease	65 (71.4)
Medical history	
Anaemia	3 (3.3)
Atrial fibrillation	1 (1.1)
Diabetes mellitus	16 (17.6)
Ischaemic heart disease	5 (5.5)
Ischaemic stroke	1 (1.1)
Hypertension	43 (47.3)
Hyperlipidaemia	11 (12.1)
Myocardial infarction	1 (1.1)
Thrombosis	0 (0.0)
Treatment plans	
Concurrent chemotherapy and radiation	5 (5.5)
Chemotherapy only	75 (82.4)
Radiotherapy only	5 (5.5)
Not on chemotherapy or radiotherapy	6 (6.6)

Table II. Distribution of the haemoglobin level at the initiation of epoetin alfa therapy.

Haemoglobin level at initiation of epoetin alfa therapy (g/dL)	No. (%) of patients (n = 91)
7.0–7.4	6 (6.6)
7.5–7.9	12 (13.2)
8.0–8.4	16 (17.6)
8.5–8.9	20 (22.0)
9.0–9.4	7 (7.7)
9.5–9.9	18 (19.8)
10.0–10.4	6 (6.6)
10.5–10.9	3 (3.3)
11.0–11.4	0
11.5–11.9	2 (2.2)
12.0–15.0	1 (1.1)

11 patients (12.1%) had their baseline iron blood levels assessed, and 13 patients (14.3%) had their baseline folate and Vitamin B12 blood levels assessed before epoetin alfa was prescribed. Overall, 53 patients (58.2%) who were prescribed iron therapy were prescribed folic acid concurrently with epoetin alfa. Six patients (6.6%) were detected to have a low iron blood level and only two patients received an appropriate iron supplement. Oral iron

Table III. Blood pressure monitoring among hypertensive epoetin alfa patients.

Blood pressure monitoring	No. (%) of patients at initiation of epoetin alfa with:	
	Controlled hypertension (n = 29)	Uncontrolled hypertension (n = 14)
Prescribed blood pressure medication(s)	24 (55.8)	14 (32.6)
Not prescribed blood pressure medication(s)	5 (11.6)	NA
Blood pressure monitoring frequency		
Not performed	12 (27.9)	2 (4.7)
Every week	3 (7.0)	1 (2.3)
Every two weeks	2 (4.7)	4 (9.3)
Every month	12 (27.9)	7 (16.3)

NA: not applicable

gluconate was the most commonly prescribed iron therapy among patients receiving epoetin alfa. To note, intravenous iron therapy was not administered to any patients.

At the initiation of epoetin alfa, approximately half of the patients (47.3%) manifested hypertension. Hypertension was uncontrolled in 14 patients (32.6%), even though these patients were prescribed one or more anti-hypertensive medications. The majority of the patients had their blood pressure monitored monthly by NCCS staff (Table III). After epoetin alfa was started, nine patients (9.9%) had either (1) a one-time increase in systolic blood pressure of at least 10 mmHg, or (2) exceeded the target blood pressure while they were being treated on epoetin alfa. Three of these patients had controlled blood pressure readings before epoetin alfa was started. In terms of side effects that were possibly related to the administration of epoetin alfa, an increase in blood pressure was the most commonly observed side effect, which was observed in nine patients (9.9%). No new episodes of seizures or thrombosis were reported during epoetin alfa treatment.

DISCUSSION

This study was performed at a critical time as there are increasing concerns related to the use of ESAs in cancer patients. To the best of our understanding, this study was the first retrospective study performed in Singapore that evaluated the utilisation of ESAs in cancer patients at a cancer centre. We studied the utilisation of epoetin alfa at NCCS and found that the majority of the patients responded to epoetin alfa with documented objective responses, such as an increase in haemoglobin levels as well as a decrease in transfusion requirements. The median haemoglobin level at which epoetin alfa was initiated was 8.7 g/dL, which was deemed to be an appropriate haemoglobin level to initiate epoetin alfa with respect to the safety perspective.

Currently, the initiation of ESAs is only recommended when a patient's haemoglobin is approaching or has fallen below 10 g/dL.[2,3] Initiating ESAs at haemoglobin levels above 12 g/L may lead to adverse outcomes, and this was well demonstrated in a clinical trial where locally-advanced head and neck cancer patients were started on darbepoetin when haemoglobin levels dropped below 14 g/dL in order to maintain a level of 14–15.5 g/dL. The results of this trial showed a much poorer control of locoregional disease and a decreased five-year disease-free survival rate among patients on darbepoetin compared to the placebo group.[16] In our study, only three patients were started on epoetin alfa at haemoglobin levels above 11 g/dL. However, due to the retrospective nature of this study, it was impossible to evaluate why these patients were started on epoetin alfa. However, it is important to note that symptomatic anaemia was only observed in one patient.

Full blood counts were monitored at least every two weeks for most patients, and almost half of these patients achieved a "positive" response to epoetin alfa within 2–6 weeks. Yet, there is much room for improvement to ensure that the best therapeutic outcome is achieved. For instance, almost one-third of the patients (25 patients) had an "excessive" response to epoetin alfa, whereby their haemoglobin levels had either risen by more than 1 g/dL within two weeks or exceeded 12 g/dL, but only one-third of these patients with an "excessive" response had their therapy held or discontinued. This is one area in which the utilisation of epoetin can be much improved upon. Guidelines on the appropriate dose reduction for patients who have excessive responses to epoetin alfa are available and such practices can help to cut down on unnecessary drug usage and minimise the risk of thrombosis.[2,3]

Among patients who were "poor" responders to epoetin alfa, merely two patients received the appropriate dosage adjustment for their epoetin alfa. According to established guidelines and the package insert recommendations of epoetin alfa, if the dose of epoetin alfa is unable to mount a haematological response, an increase in the dosage by 50% and close haematological monitoring are recommended to improve the efficacy of epoetin therapy.[3] There are multiple reasons that can explain the low incidence of dose escalation. It shows that clinicians have exercised

their judgment to decide whether dose escalation is necessary on a case-by-case basis.[23] Clinicians may not strictly escalate doses as per the package insert dosing, possibly due to the patient's financial constraints – after all, 70% of the patients receiving epoetin alfa are private or non-resident patients. We are only able to gain such insights by conducting a drug utilisation review, as results of a retrospective study have the ability to highlight the real-world drug utilisation. Furthermore, the variable response of our population to epoetin alfa could be due to the different intensity of chemotherapy regimens that our cancer patients have received. Most patients (71.4%) in our review manifested advanced or metastatic cancers; this could explain why these patients manifested severe anaemia and were indicated for epoetin alfa, as a majority of the study population had also previously received multiple lines of chemotherapy. Some studies have suggested that the efficacy of epoetin alfa can be compromised in patients who were heavily treated.[24]

It is also important to note that none of the patients treated on epoetin alfa at NCCS had resulted in a thrombotic event. However, it was identified that cancer patients receiving ESAs are at a higher risk of developing venous thromboembolism.[25] Patient specific risk factors that can predispose epoetin alfa patients to thromboembolism were not identified; however, an evaluation of past medical history is important for general risk factors such as previous history of thrombosis, surgery or non-ambulatory state.[2,3] In our study, none of our patients had a history of venous thrombosis except for one patient who had one documented episode of ischaemic stroke. Very few patients achieved extremely high haemoglobin levels after receiving ESAs (only 30% patients had haemoglobin levels of 11–12 g/dL), which may explain why there is such a low incidence of thrombosis in our population. Nonetheless, clinicians must weigh the risks of thromboembolism in patients for whom ESAs are prescribed.

Our study has identified a number of issues that can be improved upon to maximise the beneficial outcomes of epoetin alfa. Besides assessing blood counts on a regular basis, baseline and routine blood pressure should also be controlled before epoetin alfa is initiated. Most patients had their blood pressure monitored monthly, which fit into the monthly chemotherapy cycles. If possible, blood pressure should also be well controlled before the initiation of ESAs to prevent the exacerbation of blood pressure.[26,27] Three patients' blood pressure increased and were classified as uncontrolled after epoetin alfa was initiated. As an increase in blood pressure is identified to be associated with the administration of epoetin alfa, close monitoring and appropriate intervention are essential to ensure that the patient's blood pressure is well controlled.[3]

It appears to us that routine assessment of patients' iron stores and the practice of iron supplementation are lacking. Iron supplementation is an important component of therapy with erythropoietic agents because iron is a required element for red blood cell production. Iron replacement is particularly crucial for patients who are iron deficient at the onset of treatment, but even patients who do not start out with iron deficiency often develop a functional iron deficit with the continued use of an ESA.[3] The practice of baseline and periodic monitoring of iron levels is recommended in multiple anaemia management guidelines, and such a practice can help to maximise the benefits of recombinant erythropoietin therapy. Multiple studies have documented the benefits of iron supplementation with better efficacy outcomes archived with intravenous iron supplementation.[28,29] The limitations of this retrospective study include the inability to recover missing information from patients' case notes. As the study was retrospective in nature, it was difficult to determine whether patients were manifesting chemotherapy-induced anaemia, as the anaemia could also be due to anaemia from the cancer itself. With regard to data on side effects, it was extremely difficult to capture and differentiate whether certain side effects were caused by epoetin alfa, as many could also be caused by chemotherapy.

We suggest a few strategies to improve the utilisation of ESAs in our local cancer patients. One way is to implement a treatment algorithm to guide physicians on appropriate prescribing. Furthermore, oncology pharmacists can assist physicians to monitor treatment outcomes of cancer patients who are treated on erythropoietin therapy. Multiple studies have also shown that pharmacist-managed anaemia programmes can improve clinical and economic outcomes in anaemia.[30-32] In one study, under collaborative practices with medical oncologists, pharmacists were allowed to prescribe and monitor for the dose, duration and response of ESAs. Future studies should assess whether pharmacists can assist oncologists in improving the treatment and economic outcomes of cancer anaemic patients. For many cancer patients, anaemia is one of the most noticeable and debilitating of the haematological toxicities of chemotherapy. The management of anaemia with ESAs can provide patients with symptomatic relief and decrease dependence on transfusion support. When utilised appropriately, these agents can have a significant, positive impact on the patient's overall wellbeing and quality of life. This drug utilisation evaluation can raise clinicians' awareness of the safety concerns related to ESAs. Furthermore, this evaluation has identified areas where the prescribing and monitoring practices of epoetin alfa can be improved upon in order to maximise the benefits of epoetin alfa in our cancer patients.

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