

ORIGINAL ARTICLES

Neutropenia in Asian patients with solid tumours receiving chemotherapy: A retrospective case-control study

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ABSTRACT

Aim: To compare the incidence of neutropenia and neutropenic sepsis in Asian versus Caucasian patients with solid tumours on intravenous chemotherapy.

Methods: A retrospective case-control study comparing the incidence of neutropenia and neutropenic sepsis in Asian and Caucasian patients receiving infusional chemotherapy at our unit was performed. 15 Asian and 15 Caucasian patients receiving chemotherapy between November 2012 and June 2014 were included in the study and they were matched, where possible, for age, gender, tumour type and chemotherapy regime. The primary objective was to compare the incidence of grade 4 (≤ 0.5 cells $\times 10^9/L$) neutropenia and neutropenic sepsis. The secondary objective was to compare the incidence of grade 2 (≤ 1.5 cells $\times 10^9/L$) neutropenia and neutropenic sepsis.

Results: There was no significant difference in the proportion of Asian and Caucasian patients who developed grade 4 neutropenia (33.3% vs. 20% of patients; $P = .409$) or neutropenic sepsis (20% vs. 6.7%; $P = .283$). However, there was a trend towards a greater proportion of Asian patients developing grade 2 neutropenia (66.7% vs. 33.3%; $P = .068$) which was associated with a significantly greater proportion of Asian patients developing grade 2 neutropenic sepsis (40% vs. 6.7%; $P = .031$).

Conclusion: This small-scale study suggests that Asian patients may suffer from an increased propensity towards neutropenia and neutropenic sepsis when receiving infusional chemotherapy emphasising the need for further research in this area. In particular, the role of prophylactic supportive therapy, such as G-CSF, in Asian patients needs to be determined.

Key Words: Chemotherapy, Neutropenia, Sepsis, Asian, Caucasian

1. INTRODUCTION

Neutropenic sepsis is a potentially fatal complication of anti-cancer treatment. Mortality rates ranging between 2% and 21% have been reported in adults.^[1] Neutropenic sepsis is also associated with significant morbidity including hospitalisation,^[2] treatment delay,^[3] dose reduction^[4] and potentially

disease progression.

Research has identified a number of risk factors for the development of neutropenic sepsis which can largely be categorised into genetic (polymorphisms) and acquired (increasing age, female gender, poor performance status, advanced disease, various comorbidities, low body surface area to body

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mass index, low baseline blood cell counts).^[5] However, there remains a paucity of research regarding the effect of ethnicity on the development of neutropenia and neutropenic sepsis. Anecdotally, oncologists and haematologists often comment that patients of Asian origin demonstrate a greater degree of myelosuppression than their Caucasian counterparts, however at present there is no evidence to support this theory.^[3] The aim of our study was to compare the incidence of neutropenia and neutropenic sepsis in Asian and Caucasian patients receiving infusional chemotherapy.

2. METHODS

A retrospective review of patients receiving infusional chemotherapy between November 2012 and June 2014 was performed. We identified 15 Asian and 15 Caucasian patients for inclusion into the study. Caucasian patients were selected by matching age, sex, tumour type and chemotherapy regime, where possible, with those of Asian patients. Patients were classified as being of Asian origin if they were of Indian (n = 11), Pakistani (n = 1) or Chinese (n = 3) extraction whereas Caucasian patients were those of European extraction (n = 15). Accurate determination of country of extraction was possible because 2 of the authors (DA, KC) were responsible for regularly administering chemotherapy to all patients included in the study. Although hospital records, which document self-reported race, were also reviewed, this data was often incomplete. In cases of ambiguity over the patient's country of extraction, the patient was excluded from the study. There were no patients of Afro-Caribbean extraction included in this study. Patients were excluded if their first cycle of chemotherapy was given before the start of the study period. Full blood counts taken prior to the commencement of each chemotherapy session were used to determine the extent of myelosuppression in each ethnicity group. Hospital pharmacy records were used to determine cycle numbers and whether patients received granulocyte colony stimulating factor (G-CSF) (filgrastim or pegylated filgrastim).

Table 1. Neutropenia grading according to the National Cancer Institute common toxicity criteria, adapted from Crawford *et al.* (2004)

Grade	Absolute neutrophil count (cells × 10 ⁹ /L)
0	Within normal limits
1	1.5 ~ 2.0
2	1.0 ~ 1.5
3	0.5 ~ 1.0
4	< 0.5

The primary objective was to compare proportion of patients admitted with severe neutropenia and neutropenic sepsis.

Grade 4 neutropenia (counts ≤ 0.5 cells × 10⁹/L) was used for the primary outcome measure. Neutropenia was graded according to the National Cancer Institute common toxicity criteria (see Table 1). The National Institute of Health and Clinical Excellence^[1] also define neutropenic sepsis as a neutrophil count of ≤ 0.5 cells × 10⁹/L in the presence of pyrexia (temperature > 38 degrees) or other signs / symptoms consistent with clinically significant sepsis in any patient receiving anticancer therapy.^[1]

The secondary objective was to compare patient cohorts using a less stringent definition of neutropenia (grade 2 neutropenia, which is defined as counts ≤ 1.5 cells × 10⁹/L). Specifically the proportion of patients developing grade 2 neutropenia as well as the proportion of patients developing grade 2 neutropenic sepsis were studied.

Additionally we studied the cycle number in which neutropenia was first observed. The proportion of patients suffering a second episode of neutropenia < 1.5 × 10⁹/L during the same course of chemotherapy (*i.e.* after recovery from their first episode of neutropenia) was also studied.

Statistical analysis

Chi-squared analysis was used to compare categorical variables and an independent samples *t*-test used to compare continuous variables. All results were compared and expressed as Asian patients relative to Caucasian patients. A *P* value of < .05 was used to determine statistical significance. SPSS version 22 (IBM, USA) was used to perform all statistical analyses.

3. RESULT

Patients had a mean age at first chemotherapy infusion of 52.3 years (range 25.4-73.7 years) and were predominantly female (n = 24). The most common cancer type was breast cancer (n = 11) and the most common chemotherapy regime (n = 10) was a combination of fluorouracil, epirubicin and cyclophosphamide (FEC) with or without docetaxel. Table 2 shows demographics by ethnicity group.

3.1 Primary outcomes

There was no significant difference in the proportion of Asian and Caucasian patients admitted with grade four neutropenia (5/15 Asian *vs.* 3/15 Caucasian patients; 33.3% *vs.* 20%; *P* = .409) or neutropenic sepsis (3/15 *vs.* 1/15; 20% *vs.* 6.7%; *P* = .283).

3.2 Secondary outcomes

There was a trend towards a greater proportion of Asian patients developing grade 2 neutropenia (10/15 *vs.* 5/15; 66.7% *vs.* 33.3%; *P* = .068) although this failed to reach statistical

significance. However, a significantly a greater proportion of Asian patients developed grade 2 neutropenic sepsis (6/15 vs. 1/15; 40% vs. 6.7%; $P = .031$).

Grade 2 neutropenia in Asian patients did not develop at

later cycle numbers (2.6 vs. 3.4 cycles; $P = .445$) or at a significantly greater number of days post 1st chemotherapy infusion (77.1 vs. 66.4 days; $P = .805$). There was also no difference in the proportion of patients developing a second episode of grade 2 neutropenia (38.5% vs. 42.9%; $P = .848$).

Table 2. Cohort demographics dichotomised by ethnicity

	Asian (n = 15)	Caucasian (n = 15)
Median age (range), years	52.1 (25.4-60.2)	55.8 (30.9-73.7)
Female sex, N (%)	12 (80)	12 (80)
Cancer type, N (%)		
Breast	6 (40)	5 (33.3)
Ovarian	4 (26.7)	4 (26.7)
Urological	1 (6.7)	2 (13.3)
Colorectal	1 (6.7)	2 (13.3)
Unknown primary	1 (6.7)	1 (6.7)
Other	2 (13.3)	1 (6.7)
Chemotherapy regime, N (%)		
Platinum-based +/- Gemcitabine / Paclitaxel / 5-FU	7 (46.7)	6 (40)
FEC/FEC-T	5 (33.3)	5 (33.3)
Caelyx	2 (13.3)	2 (13.3)
Folfox	1 (6.7)	2 (13.3)
On non-first line chemotherapy, N (%)	5 (33.3)	2 (13.3)
On G-CSF therapy, N (%)	8 (53.3)	7 (46.7)

Note. 5-FU: 5-Fluorouracil; FEC: 5-Fluorouracil, Epirubicin, Cyclophosphamide; FEC-T: 5-Fluorouracil, Epirubicin, Cyclophosphamide, Taxotere.

4. DISCUSSION

This study has shown that Asian patients do not develop a greater incidence of severe neutropenia or severe neutropenic sepsis, when compared with their Caucasian counterparts. However, they do suffer an increased propensity towards less severe grades of neutropenia including those associated with an increased rate of sepsis. Furthermore, in our cohort, this propensity towards neutropenia cannot be explained by Asian patients receiving more cycles of chemotherapy. To our knowledge this is the first study to compare the incidence of myelosuppression in Asian and Caucasian patients.

The findings from this study are important because the presence of neutropenia, and particularly neutropenic sepsis,^[5] are associated with numerous adverse clinical events including the need for hospitalisation, increased treatment costs, the need for dose reductions and delays to treatment. These complications impact not only on the efficacy of chemotherapy^[6] but also have a detrimental impact on the patient's quality of life.

Pharmacoethnicity describes ethnic diversity in drug response and toxicity. Although not extensively studied, pharmacoethnicity has received some attention in recent years

with respect to drugs used in oncology.^[7] Factors responsible for pharmacoethnicity can broadly be classified as genetic or environmental, however most of the previous research in this area has focused on genetic factors. Wong *et al.* showed that in breast cancer patients receiving Gemcitabine and Carboplatin chemotherapy the presence of certain genetic polymorphisms (SLC2A8A1 + 1528TT and TYMS + 1494ins6/ins6) which are more commonly found in Asian patients (prevalence 40% in Asians versus 0.5% in Caucasians) is associated with an significantly increased rate of myelotoxicity.^[8] Furthermore Uesaka reported that the addition of oral fluoropyrimide to gemcitabine chemotherapy selectively improved outcomes in Japanese patients but not in Caucasian patients which was attributed to ethnic differences in drug metabolism and clearance.^[9] Environmental causes for pharmacoethnicity in cancer patients include factors such as rates of smoking, alcohol use as well as dietary habits.^[7]

NICE does not currently recommend G-CSF be routinely used for the prevention of neutropenic sepsis in patients receiving infusional chemotherapy unless G-CSF is an integral part of the chemotherapy regime.^[11] The results of this study are not sufficient to support the routine use of G-CSF amongst Asian patients receiving chemotherapy however this

may be something that requires further investigation. The American Society of Clinical Oncology guidelines recommend that G-CSF should be used when the risk of febrile neutropenia is greater than 20% and in our study 20% of Asian patients developed grade 4 neutropenic sepsis.^[10] Furthermore, from an economic standpoint this could prove beneficial. The average cost at our hospital for a three day admission related to neutropenic sepsis costs approximately £2,000. In contrast, the cost per neupogen (filgrastim) injection is approximately £80 which is given as a 3-day course (£240) and on average patients at our centre required about 6 courses (£1,440). However, cost implications aside, the avoidance of significant neutropenia during chemotherapy is associated with a number of benefits for patients such as improved psychological wellbeing, avoiding hospital admission and preventing treatment delay.

Both increasing age and type of chemotherapy regime are known to influence rates of neutropenia.^[3] For this reason we matched patients for age and type of chemotherapy regime as closely as possible between our two study cohorts. Furthermore there was no difference in the proportion of patients receiving G-CSF between our 2 groups.

The main limitations of this study are two-fold; the small sample size and the methods used to define ethnicity. Defining ethnicity is a problem common to many studies. In the current study, patients were classified as being of Asian ethnicity if their extraction was from the Asian subcontinent. Religion was not taken into consideration. A detailed analysis of each patient's ancestry to determine their background

however was not performed and hence we were not able to control for the effects of genetic dilution. This is something that future studies could try to address. Some studies have also used "self-reported race" as a marker of ethnicity. We did not use this method unless when the data was already available from hospital records. All participants were living in the United Kingdom for the duration of their chemotherapy which would of reduced the influence of geographical variation, a known environmental pharmacoethnicity factor. Finally, this study only compared Asian patients against Caucasian patients and did not include patients of Afro-caribbean origin. Given the incidence of benign neutropenia amongst African individuals^[11] it will be interesting to determine if a similar relationship exists in this patient population.

5. CONCLUSION

This small-scale study suggests that Asian patients suffer from an increased propensity towards neutropenia and neutropenic sepsis when receiving infusional chemotherapy. Larger scale studies are needed to determine the true significance of this finding and determine whether Asian patients would benefit from prophylactic supportive therapy such as G-CSF.

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CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interests.

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