Validation of a predictive model that identifies patients at high risk of developing febrile neutropaenia following chemotherapy for breast cancer

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Background: We have previously developed a predictive model that identifies patients at increased risk of febrile neutropaenia (FN) following chemotherapy, based on pretreatment haematological indices. This study was designed to validate our earlier findings in a separate cohort of patients undergoing more myelosuppressive chemotherapy supported by growth factors.

Patients and methods: We conducted a retrospective analysis of 263 patients who had been treated with adjuvant docetaxel, adriamycin and cyclophosphamide (TAC) chemotherapy for breast cancer. All patients received prophylactic pegfilgrastim and the majority also received prophylactic antibiotics.

Results: Thirty-one patients (12%) developed FN. Using our previous model, patients in the highest risk group (pretreatment absolute neutrophil count $\leq 3.1 \times 10^9/l$ and absolute lymphocyte count $\leq 1.5 \times 10^9/l$) comprised 8% of the total population and had a 33% risk of developing FN. Compared with the rest of the cohort, this group had a 3.4-fold increased risk of developing FN ($P = 0.001$) and a 5.2-fold increased risk of cycle 1 FN ($P < 0.001$).

Conclusions: A simple model based on pretreatment differential white blood cell count can be applied to pegfilgrastim-supported patients to identify those who are at higher risk of FN.

Key words: chemotherapy, febrile neutropaenia, risk models

introduction

Febrile neutropaenia (FN) is the most common life-threatening toxicity encountered in patients undergoing adjuvant chemotherapy for breast cancer. While with early identification and treatment, deaths from FN are thankfully rare, there remains significant morbidity and cost associated with the development of this complication [1]. The introduction of taxanes and coadministration of targeted therapies have resulted in chemotherapy regimens that are considerably more myelosuppressive than previous combinations [2, 3]. Identifying patients who are at increased risk of FN is therefore of growing importance to medical oncologists who treat patients with breast cancer.

We have previously reported that the pretreatment differential white blood cell count can be used to predict for excessive myelosuppression in patients receiving adjuvant FEC (5-fluorouracil, epirubicin, cyclophosphamide) chemotherapy [4]. In this study, patients were divided into five groups based on quintiles of the absolute neutrophil count (ANC) and the absolute lymphocyte count (ALC). These groups were then combined in rank order. Patients in the group with the lowest values (both ANC $\leq 3.1 \times 10^9/l$ and ALC $\leq 1.5 \times 10^9/l$) were at significantly increased risk of developing a neutropaenic event (52%), receiving suboptimal dose intensity (36%) or developing FN (21%) compared with the rest of the cohort [4]. Here, we attempt to validate these findings in a separate population of patients treated with a taxane-based chemotherapy regimen. Unlike other studies that have sought to identify predictive factors for chemotherapy-induced neutropaenia, a unique feature of this report is that all patients received primary prophylaxis with pegfilgrastim and that the majority also received prophylactic antibiotics. Indeed, the primary rationale for many previous studies in this field has been to identify patients who might benefit from myeloid growth factors [5, 6]. As our findings are based on a group of patients receiving optimal supportive care [7], they are particularly pertinent to present day practice.

methods

Using our patient information system, an electronic database through which chemotherapy is prescribed, we retrospectively identified 280 consecutive patients who had been treated with six cycles of adjuvant...
docetaxel, adriamycin and cyclophosphamide (TAC) chemotherapy for breast cancer in the period 2007–2009. Seventeen patients were excluded from the analysis due to failure to complete the full treatment course or irretrievable blood counts, leaving 263 patients for further assessment. The regimen employed (docetaxel 75 mg/m², adriamycin 50 mg/m² and cyclophosphamide 500 mg/m² ad/minister i.v. every 3 weeks) has been reported previously [8]. Patient demographics and tumour characteristics are given in Table 1. All patients received primary growth factor prophylaxis with a single s.c. dose of pegfilgrastim (6 mg), given 24 h after chemotherapy. Dexamethasone premedication (8 mg twice daily for 3 days starting 1 day before chemotherapy) was used to minimise the risk of capillary leak syndrome secondary to docetaxel. Neither a priori dose reductions nor body surface area (BSA) capping were employed in this series [9]. At our institution, a dose-banding algorithm is used to facilitate the reconstitution of drugs in the cytotoxic pharmacy. The actual doses of chemotherapy delivered are within 5% of the calculated doses based on the BSA [10]. Due to concerns about engendering bacterial resistance and the previous high incidence of nosocomial Clostridium difficile infections at our institution, the first 78 patients treated did not receive prophylactic antibiotics. This policy was changed early in 2008 and the remaining 185 patients were given levofloxacin, 500 mg once daily for 7 days starting on day 4 after chemotherapy.

Throughout the period of this study, a departmental policy for the prescription of chemotherapy was in operation. Baseline blood counts pre-cycle 1 were carried out before the commencement of the steroid premedication. For subsequent cycles, blood counts were checked no earlier than 48 h prechemotherapy. Each cycle was delivered if the ANC was ≥1.5 × 10⁹/l, platelet count was ≥100 × 10⁹/l and there were no excessive (grade 3) non-haematological toxic effects. For the purposes of this analysis, we have employed the definition of FN recommended by the European Society of Medical Oncology, namely a temperature ≥38.5°C in a patient with an ANC <0.5 × 10⁹/l [11]. Neutropaenic sepsis was defined as the presence of the diagnostic features of FN with additional clinical signs of a systemic inflammatory response syndrome such as tachycardia (>90 beats per minute), hypotension (systolic blood pressure <90 mmHg), oliguria or mental confusion [12]. The Gloucestershire Oncology Centre has a dedicated neutropaenic ward and 24-h helpline to facilitate the prompt treatment of patients with chemotherapy-related emergencies. FN was managed in all patients by admission to hospital and administration of piperacillin/tazobactam with gentamicin, supplemented by other anti-infectives on the basis of clinical features or microbiological culture results. After an episode of FN or the development of severe (grade 3) non-haematological toxicity, the doses of all chemotherapy drugs were reduced by 20%. No patient received concomitant radiotherapy and endocrine treatment was only commenced after completion of chemotherapy.

This retrospective study was approved by the Departmental Research and Audit Committee. Group comparisons for continuous blood count variables were carried out using Student’s t-test. Chi-square tests were used to determine the significance of differences between categorical variables. All tests of significance were two tailed and for continuous variables, the levels of significance assume equal variances. Statistical analyses were carried out using SPSS version 10.0 (SPSS, Chicago, IL).

**Results**

Thirty-one patients (12%) developed FN (2 patients had two episodes). As illustrated in Figure 1, FN occurred more frequently during the first cycle of the treatment course. In patients developing FN, 94% had presented by day 8 post chemotherapy (Figure 2). The median ANC nadir recorded for patients with FN was 0.08 × 10⁹/l and recovery to a neutrophil count >1.0 × 10⁹/l was achieved by day 11 in 91% of episodes. Ninety-seven per cent of patients with FN had an elevated C-reactive protein with the median maximum level being 63 mg/l (range 6–377 mg/l). In 25 episodes (76%), the criteria for a diagnosis of neutropaenic sepsis were met. Positive blood cultures were obtained in only three cases (9%). All were Gram-positive organisms (coagulase-negative staphylococci in two patients and a diphtheroid species in one patient) obtained in patients with central venous catheters. In five other patients, the source of infection was clinically evident (dental infections in three patients, cellulitis in one patient and herpes varicella-zoster infection in one patient). Only one case of _C. difficile_

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**Table 1. Patient demographics, tumour characteristics and pretreatment haematological indices**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>48 (27–66)</td>
</tr>
<tr>
<td>Node positive</td>
<td>243</td>
</tr>
<tr>
<td>Node negative</td>
<td>18</td>
</tr>
<tr>
<td>Node status unknown</td>
<td>2</td>
</tr>
<tr>
<td>Grade 1</td>
<td>9</td>
</tr>
<tr>
<td>Grade 2</td>
<td>95</td>
</tr>
<tr>
<td>Grade 3</td>
<td>152</td>
</tr>
<tr>
<td>Grade unknown</td>
<td>7</td>
</tr>
<tr>
<td>ER positive</td>
<td>197</td>
</tr>
<tr>
<td>ER negative</td>
<td>63</td>
</tr>
<tr>
<td>ER unknown</td>
<td>3</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>66</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>17</td>
</tr>
</tbody>
</table>

Pretreatment haematological indices (median and range)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (×10⁹/l)</td>
<td>6.90 (3.8–19.5)</td>
</tr>
<tr>
<td>Absolute neutrophil count (×10⁹/l)</td>
<td>4.3 (1.6–17.9)</td>
</tr>
<tr>
<td>Absolute lymphocyte count (×10⁹/l)</td>
<td>1.9 (0.3–4.4)</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

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**Figure 1.** The timing of febrile neutropaenia episodes during the course of chemotherapy. Two patients developed two episodes of febrile neutropaenia (FN) in separate cycles and these have been recorded separately.
associated diarrhoea was reported and this developed in a neutropaenic patient who had not been treated with prophylactic antibiotics. There was no mortality from FN but one death from necrotising fasciitis occurred in a non-neutropaenic patient.

The frequency of FN in patients receiving prophylactic antibiotics was significantly lower than in those that did not (8% versus 22%, *P* = 0.001). The protective effect of antibiotics was most evident in the first three cycles (5% versus 17%, *P* = 0.002) in keeping with the greater frequency of FN in these cycles (Figure 1). In contrast, the absolute benefit derived from the use of antibiotics in the latter three cycles of chemotherapy was much reduced (3% versus 6%, *P* = 0.15), reflecting the lower frequency of FN in these cycles.

Pretreatment ANC and ALC were not by themselves correlated with the frequency of FN (*P* = 0.95 and 0.33, respectively). However, when patients were combined into five groups based on quintiles of ANC and ALC as described previously [4], there were highly statistically significant differences in the risk of any cycle FN (*P* = 0.018) and cycle 1 FN (*P* = 0.004) between each group (Table 2 and Figure 3). Patients in group V (pretreatment ANC ≤ 3.1 × 10⁹/l and ALC ≤ 1.5 × 10⁹/l) had a 3.4-fold increase in any cycle FN (*P* = 0.001) and a 5.2-fold increase in cycle 1 FN (*P* < 0.001) compared with the rest of the cohort. Simply using group V versus groups I–IV to predict for episodes of FN, results in a model with a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 0.23, 0.94, 0.33 and 0.90, respectively. To predict for FN in cycle 1, the performance of the model was slightly improved with a sensitivity, specificity PPV and NPV of 0.31, 0.94, 0.24 and 0.95, respectively. The model was also able to identify patients at high risk of FN, irrespective of the use of antibiotics. Thus for the cohort receiving prophylactic antibiotics (*n* = 185), patients in group V had a 3.3-fold increased risk of any cycle FN (*P* = 0.04) and a 6.2-fold increased risk of cycle 1 FN (*P* = 0.02). Similarly for the cohort in which prophylactic antibiotics were omitted (*n* = 78), patients in group V had a 3.1-fold increased risk of any cycle FN (*P* = 0.02) and a 4.3-fold increased risk of cycle 1 FN (*P* = 0.01).

To investigate further the association between pretreatment haematological indices and FN, we studied a subset of patients (*n* = 36) who had retrievable day 7 neutrophil ‘nadir counts’ carried out during the first cycle of chemotherapy. There was a weak correlation between the day 7 neutrophil count and pretreatment ALC (*r* = 0.34, *P* = 0.03). Furthermore, patients who went on to develop grade 4 chemotherapy-induced neutropaenia (ANC < 0.5 × 10⁹/l) on day 7 were found to have a lower pretreatment ALC (1.6 × 10⁹/l versus 2.2 × 10⁹/l, *P* = 0.04).

**Discussion**

FN is an increasingly common side-effect of modern chemotherapy regimens. In addition to the drugs used, the frequency of FN is also dependent on a number of patient-related factors. For example, age over 65 years, advanced disease, poor performance status, co-morbid illness and female status have all been reported to be associated with increased risk of severe myelosuppression [7]. Clinical guidelines incorporating these factors have been developed to help identify patients at increased risk of FN and thereby permit targeted prophylaxis with myeloid growth factors or antibiotics [7]. However, it is self-evident that the majority of these factors are not relevant to the group of patients receiving adjuvant therapy for early breast cancer. Other models which predict for the risk of developing FN on the basis of a nadir count obtained during cycle 1 have also been developed [13, 14]. Unfortunately, they too are of limited clinical utility since, as shown in Figure 1, the risk of FN is overwhelmingly skewed towards the first cycle of treatment.

**Table 2.** The risk of FN according to patient group

<table>
<thead>
<tr>
<th>Group</th>
<th>ANC (×10⁹/l)</th>
<th>ALC (×10⁹/l)</th>
<th>Number</th>
<th>Number with FN in any cycle</th>
<th>Number with FN in cycle 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt;5.2</td>
<td>&gt;2.4</td>
<td>99 (38%)</td>
<td>13 (13%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>II</td>
<td>≤5.2</td>
<td>≤2.4</td>
<td>64 (24%)</td>
<td>5 (8%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>III</td>
<td>≤4.4</td>
<td>≤2.1</td>
<td>47 (18%)</td>
<td>4 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>IV</td>
<td>≤3.8</td>
<td>≤1.8</td>
<td>32 (12%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>V</td>
<td>≤3.1</td>
<td>≤1.5</td>
<td>21 (8%)</td>
<td>7 (33%)</td>
<td>5 (24%)</td>
</tr>
</tbody>
</table>

*There were statistically significant differences between the groups for FN in any cycle (*P* = 0.018) and FN in cycle 1 (*P* = 0.004). ANC, absolute neutrophil count; ALC, absolute lymphocyte count; FN, febrile neutropaenia.
We have previously reported that a strong correlation exists between pretreatment differential white blood cell count and the risk of excessive chemotherapy-induced neutropenia [4]. By combining quintiles of ANC and ALC, we developed a simple model that stratified patients according to the chance of developing a neutropaenic event. In the group of patients with the lowest values of both ANC and ALC, which comprised 6% of the total population, the risk of developing FN was 21% compared with 6% for the rest of the cohort. Many other groups have also reported that the pretreatment white blood cell count correlates with the risk of developing FN or severe neutropenia [5, 6]. More specifically, baseline lymphopaenia [15, 16] and baseline monocytopenia [17] have been found to predict for FN in patients undergoing chemotherapy.

At our institution, the TAC regimen was introduced for the adjuvant treatment of women with node-positive breast cancer in 2007. While this regimen is more efficacious, it is also considerably more myelosuppressive than previous combinations. For example, in the registration trial when TAC was used without primary growth factor prophylaxis, the incidence of FN was 25% [8]. Therefore, in keeping with practice guidelines [7], we routinely prescribed pegylated granulocyte-colony stimulating factor (G-CSF, TAC) and more latterly prophylactic antibiotics with this regimen. The impact of these interventions on the risk of FN was demonstrated by a study, which augmented the intensity of supportive treatments by stepwise protocol amendments [18]. The frequency of FN in the groups receiving either prophylactic antibiotics alone, prophylactic pegylated granulocyte-colony stimulating factor (G-CSF), TAC regimen is associated with a 22% rate of FN [19], perhaps reflecting heterogeneity between different patient populations.

The overall risk of FN seen in our series was 12%. It is clear that, despite the use of pegylated granulocyte-colony stimulating factor (G-CSF), the risk of FN with TAC remains significant. This is in keeping with the mechanism of action of G-CSF which, while it stimulates proliferation of the neutrophil lineage thereby shortening the duration of neutropenia, has less effect on the depth of the neutrophil nadir [20]. It has long been recognised that the susceptibility to infections is inversely proportional to the ANC [21]. The TAC regimen is associated with early profound neutropaenia which, although short-lived, puts patients at significant risk of infective complications (Figure 2).

Our data have confirmed the critical importance of prophylactic antibiotics in reducing the risk of FN associated with the TAC regimen. Primary anti-infective prophylaxis was not supported in guidelines issued by the Infectious Diseases Society of America due to concerns about increasing antibiotic resistance, which might both compromise the success of treating FN and encourage the spread of multiresistant strains in the community [22]. However, more recent level I evidence confirms that such prophylactic treatment significantly reduces the risk of FN and infection-related mortality in patients receiving chemotherapy for solid tumours [23, 24]. Furthermore, earlier concerns about antibiotic resistance do not appear to be substantiated by recent literature. Thus, while prophylactic antibiotics can cause colonisation of individual patients with resistant organisms, this increase in quinolone-resistant Gram-positive and Gram-negative isolates did not adversely affect outcomes [24].

The disproportionately high number of cases of FN in the first cycle of chemotherapy illustrated in Figure 1 has also been reported in many previous studies [4, 23, 25]. We found that the absolute benefit derived from the use of prophylactic antibiotics was most marked in the early cycles and considerably reduced in cycles 4–6, reflecting differences in the frequency of FN through the treatment course. Interestingly, G-CSF has diminished effectiveness at ameliorating the duration and depth of neutropenia in cycle 1 compared with subsequent cycles [20, 26, 27]. In the light of these two observations, we think that a risk-adapted approach to antibiotic prophylaxis may prove optimal [25]. For example, only the early high-risk cycles could be covered deriving most of the benefit from this approach while addressing some of the concerns regarding antibiotic stewardship.
This study has validated our earlier observation that a simple model based on the differential white blood cell count can be used to identify patients at high risk of FN. As shown in Table 2 and Figure 3, patients in group V are at significantly greater risk of developing FN than the rest of the cohort (group I–IV). It is interesting to speculate as to the possible mechanism underlying these observations. The protective effect of higher ANC and ALC might derive from enhanced cellular immunity. Borg et al. [28] showed that subsets of peripheral blood lymphocytes, specifically the CD4 positive helper T cells are predictive for the risk of developing FN. Alternatively, higher baseline ANC and ALC might simply be indicative of a more substantial bone marrow reserve of progenitor stem cells. On the basis of the correlation of ALC with neutrophil nadir count and the strong association with treatment delays [4], we consider the latter hypothesis to be more plausible.

It is clear that better strategies are needed to counter the early neutropaenia associated with the TAC regimen, particularly in the high-risk group of patients where the risk of FN exceeds 30% in spite of the use of optimal supportive therapy. Given the early presentation of FN following chemotherapy, one intuitive approach would be to commence pegfilgrastim earlier. Burris et al. [19] have reported a randomised phase II study of same day versus next day administration of pegfilgrastim. Paradoxically, same day administration was associated with earlier, deeper and longer neutropaenia as well as higher rates of FN [19]. An alternative strategy is to individualise the dose of pegfilgrastim. A dose of 100 mcg/kg was shown to be effective prophylaxis and well tolerated [26]. The use of the 6 mg fixed dose while convenient might not afford as complete protection to heavier patients due to an effective decrease in dose per kilogram. However, in our data, we did not see any association of weight and risk of FN.

A second strategy that could be employed to reduce the risk of FN in the high-risk subgroup is to intensify the antibiotic prophylaxis. As most patients with FN present in the first week, starting antibiotic prophylaxis on day 4 post chemotherapy may be too late to achieve stable tissue concentrations. Broader spectrum antibiotic coverage might also be helpful. In our series, the frequency of documented bacteraemia in patients with FN was low (9%) perhaps reflecting the use of prophylactic antibiotics [23]. However, all the confirmed isolates were Gram-positive organisms in patients with central venous access devices. Coagulase-negative staphylococci have emerged as one of the most commonly cultured organisms in neutropaenic patients receiving fluoroquinolone prophylaxis [29]. A meta-analysis has shown that the effectiveness of quinolone prophylaxis can be improved further by adding agents with enhanced Gram-positive cover [29]. This strategy would appear appropriate for the high-risk group, particularly when central venous catheters are used.

In summary, we have validated our earlier model in a separate cohort of breast cancer patients treated with a different chemotherapy regimen and supportive strategies. While the high-risk subgroup constitutes only a small proportion of the overall population undergoing chemotherapy, they remain at substantial risk of developing FN despite the use of pegfilgrastim. These patients should be monitored closely and potentially are candidates for broader spectrum anti-infective prophylaxis, particularly in the early cycles of chemotherapy. However, it must be acknowledged that, although a high-risk subgroup can be identified, the accuracy of this model in predicting FN is limited. In addition to bone marrow sensitivity, pharmacokinetic and pharmacodynamic variations in drug clearance are likely to have a major influence on acute chemotherapy toxic effects, such as myelosuppression. Until such variations in drug exposure can be accurately quantified, a truly reliable method for predicting the risk of FN is likely to remain elusive.

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Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer

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Background: Insulin/insulin-like growth factor-I (IGF-I) signaling is a mechanism mediating the promoting effect of type 2 diabetes (DM2) on cancer. Human epidermal growth factor receptor (HER2), insulin receptor and IGF-I receptor involve the same PI3K/AKT/mTOR signaling, and different antidiabetic pharmacotherapy may differentially affect this pathway, leading to different prognoses of HER2+ breast cancer.

Methods: We reviewed 1983 consecutive patients with HER2+ breast cancer treated between 1 January 1998 and 30 September 2010. The overall survival, breast cancer-specific death rate, age, race, nuclear grade, stage, menopausal status, estrogen and progesterone receptor status, body mass index and classes of antidiabetic pharmacotherapy were analyzed.

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