Reviewer's report

Title: Multivariable regression analysis of febrile neutropenia occurrence in early breast cancer patients receiving chemotherapy assessing patient-related, chemotherapy-related and genetic risk factors

Version: 2

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Reviewer: Eric J Bow

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1.0 General Comments

Pfeil and colleagues have submitted a well-written analysis of potential predictors for neutropenic fevers among 994 consecutive early stage breast cancer patients receiving neo-adjuvant or adjuvant FEC100-based therapy from a single centre in Leuven, Belgium. The authorship has considerable experience in publishing predictive models for neutropaenic fevers in lymphoma and solid tumours. Unique to this analysis is the inclusion of single nucleotide polymorphisms as potential predictor variables.

Neutropaenic fevers occurred in 166 of the 994 subjects (16.7%, 95%CI 14.5% to 19.2%) during the course of FEC100-based chemotherapy. The majority of events occurred during cycle one (107 of 166 subjects, 64.5%, 95%CI 56.9% to 71.3%). Prophylactic haematopoietic growth factors were administered to only 15 of 994 (1.5%) subjects. A spectrum of independent variables was tested for relationship trends to the dependent variable, neutropaenic fevers. The trend was defined by a P # 0.25 in univariate analysis. Candidate variables were included in the multivariate model if the corresponding P # 0.05. The predictive value of the final models was derived from area under the receiver operator curves (AUC).

The multivariate analysis identified lower baseline platelet counts and haemoglobin, higher baseline alanine aminotransferase (ALT) levels, and a number of SNPs (rs4148350 and rs246241 in the MRP-1 gene, and rs351855 in the FGFR4 gene) as associated with the development of neutropaenic fever syndromes in any cycle. The authors noted that subjects homozygous for the rs4148350 T-allele in the MRP1 gene were at greater risk for neutropaenic fevers (80% event rate) than those homozygous (15% event rate) or heterozygous (25% event rate) for the G-allele. Subjects homozygous for the rs246241 T-allele in the MRP1 gene had a lower risk (13% event rate) than subjects homozygous (20% event rate) or heterozygous (24% event rate) at the C-allele. Subjects homozygous for the rs351855 T-allele of the FGFR4 gene had a lower risk for neutropaenic fevers (10% event rate) than those homozygous (19% event rate) or heterozygous (16% event rate) in the C-allele of the FGFR4 gene. The receiver operator curve (AUC 0.661, 95%CI 0.629 to 0.691) demonstrated modest discrimination for the model. A similar pattern of risk was observed during cycle 1 with respect to subjects homozygous at the rs4148350 T-allele in the MRP1 gene (40% event RATE) compared to homozygous (10% event rate)
or heterozygous (18% event rate) carriers of the G-allele in the MRP1 gene. The area under the ROC for neutropaenic fevers during the first cycle also showed a modest discriminating ability (AUC 0.664, 95%CI 0.633 to 0.694). The authors concluded that neutropaenic fevers were more likely in this population of adjuvant and neo-adjuvant FEC100-based chemotherapy recipients who had lower baseline platelet counts and haemoglobin levels, and who were homozygous carriers of the rs4148350 T-allele in the MRP1 gene. Conversely, a lower baseline ALT, and homozygous carriers of the rs246221 T-allele in the MRP1 gene or rs351855 T-allele in the FGRR4 gene predicted a lower febrile neutropaenia risk. The authors speculate that subjects in the former group might be candidates for infection prevention strategies. They further conclude that the high negative predictive value of the model predicted those subjects for whom the neutropaenic fever event rate would be too low to warrant such interventions.

Overall this is a negative study. The multivariate model was insufficiently predictive to discriminate those at highest risk for neutropaenic fever events. They were able to demonstrate some value for the SNP analysis, however. Whilst a broad spectrum of candidate independent variables for the analysis were evaluated, important variables associated with neutropaenic fevers such as presence of central venous access devices and mucositis were not included. Analysis of the candidate independent variables by classification (Microbiologically documented infection, clinically documented infection, and unexplained fever. International Immunocompromised Host Society. The design, analysis, and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. Report of a consensus panel. JID 1990; 161(3): 397-401) would add value to the model given the relative non-specificity of fever as a dependent variable.

These minor suggestions are offered to enhance the value of the manuscript. Overall, the submission is well-written and brings to light interesting observations.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.