

## Predicting the duration of chemotherapy-induced neutropenia: new scores and validation

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### Study Overview:

Chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) are frequently observed consequences of myelosuppressive chemotherapy. It is important to accurately predict the duration of a neutropenic episode because the risk of life-threatening complications increases with the duration. One recognised determinant of the duration of FN is the aggressiveness of the chemotherapy regimen.

A previously reported prediction model (Lalami Y, et al. *Ann Oncol* 2006;17:507-14) assigned scores to individual chemotherapy agents and determined the score of a combination regimen by adding together the individual drug scores. Values above or below a given threshold indicated a long or short expected CIN duration. However, cross-validation of this model on a new data set did not show satisfactory results. The goal of the present analysis was to develop a new and reproducible methodology for the prediction of CIN duration, based on advanced statistical tools and using only the haematological toxicity of the chemotherapy agents as input variables.

Data from 106 patients with solid tumours experiencing FN during chemotherapy in a single centre in Spain between June 1997 and October 2006 were analysed. The first episode of FN, defined as an absolute neutrophil count (ANC)  $< 0.5 \times 10^9/L$  and fever  $> 38^\circ C$ , was assessed. Duration of neutropenia was defined as the time from the first documentation of CIN until ANC recovery to  $\geq 2 \times 10^9/L$ .

### Methods:

Two types of methodology were used to predict if a patient would have a long or a short duration of CIN:

- Approaches based on weighted individual drug scores were designed.
- A second approach was based on clustering and decision trees:
  - Cluster analysis defined two groups of patients with short and long CIN duration ( $\leq 3$  days and  $> 4$  days;  $n = 77$  and  $29$ , respectively;  $p < 0.001$ ).
  - The database was enlarged by re-sampling and split into a training and a test data set.
  - A Classification and Regression Tree (CART) analysis was performed on the training set; the number of drugs with a given toxicity score were predictor variables and CIN duration was the response variable.
  - Within each group formed by the decision tree, the score was defined as the percentage of patients with a long CIN duration.

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- ROC analysis yielded a score of 30 as an optimal cut-off, where a value  $\geq 30$  indicates a long CIN duration.

#### Key Findings:

- Classification of CIN duration using weighted score-based approaches did not yield satisfactory results (sensitivity 51.5% for both scores tested; specificity 39.7% and 60.3%, respectively).
- The CART-based model had a sensitivity of 57.6% and a specificity of 69.9% when used on the test data set.
- Bootstrap analysis, a repeated sampling-based technique, was used for the purpose of validation. It revealed that in 99.4% of samples drawn from the test data set, the groups defined by the CART-based score showed statistically significant differences in the duration of CIN. For the other scores, the percentage of samples showing significant differences ranged from 9.6% to 46.8%.

#### Conclusions:

The authors concluded that approaches based on weighted scores were not able to accurately predict CIN duration in neutropenic patients. The CART-based score was superior to all other approaches, demonstrating that the use of more sophisticated statistical methods may lead to more robust prediction models able to reflect nonlinear relationships between variables.

<http://www.ncbi.nlm.nih.gov/pubmed/20610480>