ELSEVIER

Critical Reviews in Oncology/Hematology 90 (2014) 190–199

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

# Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review

Gary H. Lyman [a,*], Esteban Abella [b], Ruth Pettengell [c]

[a] *Fred Hutchinson Cancer Research Center and the University of Washington, Seattle, WA, USA*
[b] *Amgen Inc., Thousand Oaks, CA, USA*
[c] *St. George's University of London, London, UK*

Accepted 4 December 2013

## Contents



## Abstract

Neutropenia with fever (febrile neutropenia [FN]) is a serious consequence of myelosuppressive chemotherapy that usually results in hospitalization and the need for intravenous antibiotics. FN may result in dose reductions, delays, or even discontinuation of chemotherapy, which, in turn, may compromise patient outcomes. It is important to identify which patients are at high risk for developing FN so that patients can receive optimal chemotherapy while their risk for FN is appropriately managed. A systematic review of the literature was performed to gain

* Corresponding author at: Fred Hutchinson Cancer Research Center, P.O. Box 19024, M3-B232; Seattle WA 98109-1024, USA.
*E-mail address:* glyman@fhcrc.org (G.H. Lyman).

1040-8428/$ – see front matter 
http://dx.doi.org/10.1016/j.critrevonc.2013.12.006

a comprehensive and updated understanding of FN risk factors. Older age, poor performance status, advanced disease, certain comorbidities, low baseline blood cell counts, low body surface area/body mass index, treatment with myelosuppressive chemotherapies, and specific genetic polymorphisms correlated with the risk of developing FN. Albeit many studies have analyzed FN risk factors, there are several limitations, including the retrospective nature and small sample sizes of most studies.


*Keywords:* Febrile neutropenia; Risk factor; Cancer; Chemotherapy

## 1. Introduction

Chemotherapy-induced neutropenia is a common and serious clinical consequence of myelosuppressive chemotherapy. Severe neutropenia may be complicated by fever, or febrile neutropenia (FN), which often results in hospitalization and the administration of empiric broad-spectrum antibiotics. FN has been associated with considerable morbidity, mortality, and costs [1–4]. Chemotherapy-induced neutropenia and FN are also important dose-limiting side effects of myelosuppressive chemotherapy that often lead to chemotherapy reductions or treatment delays in subsequent cycles, potentially compromising treatment outcomes [5,6].

Chemotherapy regimens have been classified as having a high, intermediate, or low risk of developing FN based on prospective clinical trials of selected patients with variable capture of treatment-related toxicities including neutropenia and FN [7]. Such data have been difficult to evaluate as patients eligible for clinical trials are often highly selected and hematologic toxicities are often underreported. In addition, historically very few chemotherapy clinical trials report the delivered chemotherapy dose intensity which can vary greatly and has a direct influence on rates of toxicity [7].

Current guidelines state that chemotherapy regimens with >20% FN rate in clinical trials of chemotherapy-naïve patients are considered high risk [8–10]. Most regimens used for the treatment of adult solid malignancies are rated as intermediate risk for FN based on previous clinical trials. However, clinical practice guidelines recognize that patient risk factors may elevate FN risk and recommend the assessment of risk factors in estimating the overall risk of FN [8–10]. Furthermore, the guidelines recognize older age (particularly >65 years), previous chemotherapy or radiotherapy, pre-existing neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities (e.g., renal or liver dysfunction), and pre-existing conditions (e.g., infection) as risk factors for developing severe neutropenia [8]. Various studies have attempted to identify risk factors and develop predictive models for chemotherapy-induced neutropenia and its complications, as previously described in a review by Lyman et al. [11]. Since this systematic review was published in 2005, other reports have been published on risk factors for FN in patients with cancer receiving chemotherapy.

In this report, we describe the results of a systematic review of the literature in order to provide a more updated understanding of the risk factors associated with FN. An exhaustive search of the PubMed and Embase databases was undertaken for articles in English published between 2002 and 2012 that reported risk factors for FN. Search terms included neutropenia, agranulocytosis, FN, severe neutropenia, grade 3/4 neutropenia, risk, model(s), prediction, predictive, logistic, leukemia (lymphocytic, chronic, B-cell), lymphoma, non-Hodgkin lymphoma (NHL), cancer, neoplasm(s), carcinoma, malignancy, malignancies, metastasis, metastases, tumor, and chemotherapy. Selected studies reported univariate and/or multivariate analyses of FN risk factors in patients receiving systemic cancer chemotherapy. Reviews, meta-analyses, and case reports were excluded. While various definitions of FN were used, FN was commonly defined as an absolute neutrophil count (ANC) <1000/μL with a temperature >38 °C. Studies that reported on risk factors for hospitalization for FN were also included.

## 2. Risk factors for Febrile Neutropenia

Risk factors for FN can be classified based on patient-, treatment-, disease-, and genetic characteristics. A total of 31 studies were identified (Fig. 1). Eight studies reported univariate results only (Table 1), four reported multivariate results only (Table 2), and 16 reported on both (Table 3). Three additional studies were identified that reported on genetic markers associated with FN risk (Table 4).

### 2.1. Patient-related risk factors

#### 2.1.1. Age

Four studies found older age to be a risk factor for the development of FN [12–15]. Three of these studies were in NHL [12–14], and one study was in ovarian cancer [15]. Different cut points for age were observed depending on tumor type, with 65 years used for NHL and 60 years used for ovarian cancer.

Furthermore, one study found advanced age to be a risk factor for FN-related hospitalization [16]. In a retrospective analysis of community oncology practices in NHL, the risk of hospitalization for FN was significantly higher in patients ≥65 years old ($P < 0.001$), which was most evident during the first cycle of chemotherapy [16]. Although older patients may benefit from aggressive chemotherapy, they are usually treated with lower doses in order to minimize the occurrence of FN and its complications. It has been suggested that effective management of the risk for developing FN is important so