An in-depth analysis of adverse drug reactions associated with cancer chemotherapy, with a focus on agranulocytosis.

In contrast to Dr. Ibáñez and colleagues, we believe that the Council for International Organizations and Medical Sciences time relationship criteria are important to use (2). First, if the time window is too narrow, a delay between onset of agranulocytosis and diagnosis might obscure the causative drug. Second, some drugs associated with agranulocytosis have long half-lives and thus may be present in the body even more than 1 month after drug withdrawal. With respect to acetaminophen, an increased risk for granulocytosis has been reported (3), and this side effect is also listed in the German summary of product characteristics (4). We believe that treatment with granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor is also advantageous for primary symptomatic patients: If we analyzed the duration of neutropenia in these patients, it was borderline significantly different between treated and untreated patients if their neutrophil count nadir was less than $0.1 \times 10^9$ cells/L ($P = 0.063$) but not if it was $0.1 \times 10^9$ cells/L or greater ($P = 0.77$). If all primary symptomatic and asymptomatic patients were analyzed together, treated patients had a lower duration of neutropenia if the neutrophil count nadir was less than $0.1 \times 10^9$ cells/L ($P = 0.019$) but not if it was $0.1 \times 10^9$ cells/L or greater ($P = 0.199$).

Like Dr. Mossad, we also identified several case reports of ganciclovir-induced bone marrow damage, including agranulocytosis. However, “nonchemotherapy drug–induced agranulocytosis” generally refers to drugs causing agranulocytosis by noncytotoxic, idiosyncratic mechanisms. This categorization was difficult for some drugs. In the case of ganciclovir, the mechanism of action (inhibition of viral and human DNA polymerase), the high frequency of neutropenia listed in the summary of product characteristics (>10%), and the bone marrow suppression after overdosing also mentioned in the summary of product characteristics, suggest a nonidiosyncratic mechanism of neutropenia and agranulocytosis. Of note, other drugs, such as azathioprine, methotrexate, or colchicine, were also not included because of their known direct cytotoxic properties.

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Although the authors suggest, but do not prove, benefit from more aggressive treatment, the main goal of cardiologists is preventing deaths. Here, the role of atorvastatin should be clearly reported. 

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References


IN RESPONSE: We thank Dr. Alter, Dr. Mascitelli and Mr. Vos, and Dr. Goldstein for their careful reviews of our paper. Treatment effect was qualitatively similar in participants age 35 to 64 years and age 65 to 75 years, providing some reassurance that age does not importantly modify treatment effect. Because treatment duration was 4.9 years, some follow-up is derived from participants older than 75 years. Nonetheless, we agree that the TNT study results do not provide definitive efficacy or safety information for the 5% of the U.S. population older than 75 years. A manuscript comparing outcomes by sex is being published (1).

The primary study outcome for TNT overall, and this subanalysis in particular, was time to first occurrence of a major cardiovascular event, such as coronary heart disease death; nonfatal, non-procedure-related myocardial infarction; resuscitated cardiac arrest; and fatal or nonfatal stroke (2). Angina was not included in the primary TNT end point, and neither the overall trial nor the subanalysis was powered to determine whether small differences in total mortality were real or were simply due to chance. Apparent differences in total and noncardiovascular mortality between subgroups should be interpreted with great caution, especially in an older population in which competing causes of death (such as cancer) closer to the end of the normal life span are likely to play a larger role. Analyses by type of cancer in this and other statin trials do not show any organ specificity (3, 4). Ancillary analysis of noncardiovascular mortality in TNT (4) showed no relationship between cancer mortality and achieved low-density lipoprotein cholesterol level; participants in the lowest quintile of achieved low-density lipoprotein cholesterol (the majority taking 80 mg of atorvastatin) had the lowest cancer mortality rate (4). Data on incidence of nonfatal cancer by age subgroup are not available. Given study design and power, such analyses are unlikely to yield definitive results. We agree that our study does not support

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References


intensive lipid-lowering therapy among older or younger patients to reduce total mortality; but mortality should not be the sole measure of treatment benefit. Nonfatal cardiovascular events, such as myocardial infarction and stroke, significantly affect functional status and quality of life, worsen prognosis, and result in substantial health care expenditures. Nonetheless, a 2008 hierarchical meta-analysis of statin therapy versus placebo in patients age 65 years or older showed a reduction in all-cause mortality (relative risk reduction of 22% over 5 years) (5). We affirm our conclusion that intensive lipid-lowering therapy (atorvastatin, 80 mg daily vs. 10 mg daily) in patients age 65 years or older with established coronary heart disease prevents potentially disabling cardiovascular events, with an absolute risk reduction similar to that in younger individuals.

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Cystatin C, Renal Function, and Cardiovascular Risk

TO THE EDITOR: We read with interest the article by Menon and colleagues (1) concerning cystatin C as a cardiovascular risk factor. We believe their paper considerably increases the quality of articles published on this topic, especially because glomerular filtration rate (GFR) was measured with a reference method.

We have some comments. First, it is important to keep in mind that this study analyzes cystatin C as a cardiovascular risk factor. Because all the patients had chronic kidney disease (CKD) (GFR <55 mL/min per 1.73 m²), this study cannot be used to assert that cystatin C is definitively better than creatinine for detecting stage 3 kidney disease (GFR <60 mL/min per 1.73 m²). Regarding the study methods, the authors do not mention when cystatin C was measured in the frozen samples. Were the samples measured retrospectively? If so, are the authors sure of the stability of the cystatin C in samples frozen, for example, for more than 10 years? The authors found that cystatin C is associated with body mass index. This interesting result should be discussed in light of the recent literature (2). The authors compared cystatin C with estimated GFR to predict cardiovascular risk. Why have they not studied an equation based on cystatin C, such as the one published by Rule and colleagues (3)?

In their interesting discussion, Menon and colleagues speculate as to why cystatin C may be a better predictor of cardiovascular risk than actual GFR by iohalumate clearance. We suggest another hypothesis. Of course, cystatin C is strongly related to GFR. Nevertheless, cystatin C concentration seems also to be influenced by other factors, such as muscle mass (2), dyshormonism (hyperthyroidism increases cystatin C concentration, although it also increases GFR), and corticotherapy (which increases cystatin C concentration) (3). From comparative physiology, we know that GFR is strongly related to basal metabolic rate (4). Moreover, corticotherapy and hyperthyroidism also increase basal metabolic rate. Basal metabolic rate is also influenced by muscular mass, which is the greatest reserve of nucleated cells in the body and produces cystatin C (2). All the factors influencing cystatin C concentration could thus be related to a common “superior” factor: basal metabolic rate. This working hypothesis is further reinforced by data from the comparative physiology that suggest basal metabolic rate (like cystatin C) could be an important predictor of life span (5).

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