Reviewer's report

Title: Imbalances in serum angiopoietin concentrations are early predictors of septic shock development in patients with post chemotherapy febrile neutropenia

Version: 2 Date: 27 April 2010

Reviewer: Michael Darmon

Reviewer's report:

The manuscript has improved and the authors partly answered my comments. I still have some several concerns regarding the current manuscript. Overall, If I believe that the manuscript give interesting informations regarding Ang-1 and 2 course during neutropenia in patients who underwent SCT, I disagree with the authors conclusion regarding diagnostic performance of both Ang-2 and Ang-2/Ang-1. Indeed, beside the limitation due to the limited size of the studied population, given informations suggest that 48h after inclusion, most of the patients in the septic shock group already developed shock.

Overall, I believe that the results given in the current manuscript does not support the authors' conclusion regarding diagnostic performance of the test. I nevertheless believe that the descriptive informations given in this manuscript are of interest and deserve to be published.

Major comments:

1- Regarding multivariable analysis (Cox model in this case) I fully agree with the authors that a recent manuscript suggested to "relax the rule of ten events per variable" (Vittinghoff E et al. Am J Epidemiol 2007). However, I would like to underline that in the above mentioned manuscript, the authors suggested that a variable may be included in a model for 5 events without any dramatic increase in the model bias. However, in the current manuscript, the authors included 6 variables for 8 events. I believe that this model cannot be considered accurate.

2- A point deserve to be more clearly stated in the manuscript: When does septic shock occurs as regard with fever onset. As far as I can understand in the current manuscript, 48h after fever onset, most of the patients with septic shock were already in critical condition as regard with their SOFA score (median 7 [4-16]). If so, diagnostic performance of Ang-2 is of little interest. In the same way, authors cannot state that this test “predicted” septic shock. If septic shock occurs latter during course of the patients, I believe that this information deserve to be more clearly stated.

3- I believe that the discussion is misleading and does not accurately reflect the content of the manuscript.

a. Regarding the last paragraph (limitation). This paragraph suggests that the small sample size only limit external validity of the results. Indeed, both internal
and external validity of these results are questionable. Along the whole part evaluating performance of Ang-1 and 2 as biomarker several biases, type I and type II errors may occurs:

i. Type II error as regard to the limited sample size
ii. Type I error as consequences of the multiple comparisons.
iii. Biases due to the studied population (patients not only neutropenic but also who underwent SCT), the chosen test (Cox model without enough variables), timing at which septic shock occurs that is lacking….

b. I would urge the authors not to confound differences across the values (page 13 “This hypothesis is well illustrated in our work by the [...] trend of Ang-2/Ang-1 [...]. Patients with septic shock presented a 7 fold increase in Ang2/Ang-1 [...] as compared [...] to a 0.4 fold decrease) with statistical differences (this difference hardly reach statistical difference).

Minor comments:
1- The overall population of patients underwent either autologous or allogeneic stem cell transplantation. This point deserves to be more clearly stated in the current manuscript.
2- Please provide P value in figures 2a, 2b, 2c, 2f.

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

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.