How to calculate the MAX2 index and the average risk of toxicity for a chemotherapy regimen.

Martine Extermann

The goal of the MAX2 approach is to define the average published risk of a patient experiencing severe toxicity from chemotherapy. Severe toxicity is defined as grade 4 hematologic (H) toxicity and/or grade 3-4 non-hematologic (NH) toxicity by CTCAE criteria (presently version 3), or similar classification using the same grading of neutropenia.

The MAX2 index is defined as follows:

$$\frac{\text{Most frequent grade 4 H toxicity + most frequent grade 3-4 NH toxicity}}{2}$$

The patient risk is calculated according to the cohort type:

All ages:

$$\text{Patient risk} = \frac{\exp(-0.94 + 6.16*\text{MAX2})}{1+\exp(-0.94 + 6.16*\text{MAX2}))}$$

70 years and older

$$\text{Patient risk} = \frac{\exp(-0.96 + 8.30*\text{MAX2})}{1+\exp(-0.96 + 8.30*\text{MAX2})}$$

Practical comments

1-Typically, the MAX2 value for a regimen should be derived from 3 published studies of at least 20 patients with a reliable reporting of toxicity (i.e. in particular nadir blood counts, which most often has to be estimated from the article by an oncologist's educated guess) (some groups are more prone to do it e.g. ECOG, while others generally don't, e.g. NSABP). The most useful studies are the ones that provide a separate reporting of grade 4 ANC. If not available, refer to tips below. G4 neutropenia is typically the most frequent hematologic toxicity, although occasionally thrombopenia will be more frequent.

2-PubMed is usually an effective way to identify the articles. I go for top oncology journals first. In some cases, one might have access to a large study database and can extract the data directly.

3-I have taken to rating the level of quality of the MAX2 calculation at 5 levels

a) 3 studies with reliable G4 ANC reporting (green)
b) 3 studies with at least 1 or 2 with reliable G4 ANC reporting (yellow)
c) 3 studies with less reliable toxicity reporting (red)
d) less than 3 studies (blue)
e) extrapolated from a close regimen (brown)

4-Use of primary G-CSF/GM-CSF prophylaxis. Some regimens have that use built in (e.g. dose-dense regimens). In that case, that use is part of the basic MAX2 calculation. In other regimens, primary G-CSF may or not be given (e.g. CHOP-R). In which case, a review of several randomized studies leads to a mean 12% absolute decrease in G4 H toxicity, hence a decrease of the MAX2 value of the regimen by 0.06 for a particular patient receiving primary G-CSF.

5-Extraction of toxicity data: alopecia and lymphopenia are not counted in the derivation of the MAX2. Febrile neutropenia is considered a non-hematologic toxicity, given its unclear boundary with various infection diagnoses.

6-If no separate reporting of grade 4 ANC is available, 1 of 2 approaches can be used:

a) Use the reporting of grade 3-4 leucopenia. If the value is 30% or less, then G4 neutropenia = 0.6* G3-4 leucopenia. If the value is >30%, then G4 ANC is 0.8*G3-4 leucopenia. These are average ratios derived from studies reporting both end-points and is still fairly reliable.
b) Divide by two the reporting of grade 3-4 neutropenia. This is less reliable and would typically land the quality of the MAX2 calculation is the category c) above.

7-Tumor type usually has little impact, so I ignore it. Line of treatment might have some.

M.E.: 8/31/2009.