Survival in WM: Is OS or WM Specific Survival the right maker?

Pierre Morel

Service d'Hématologie Clinique Centre Hospitalier Schaffner, 62300 Lens, FRANCE

Censored time durations are endpoints frequently used to report the outcome of patients or the efficacy of therapy. Regardless of the primary endpoint, the description of overall survival is recommended in most studies. However disease specific survival is also frequently reported in Waldenström Macroglobulinemia (WM) studies. The clinical presentation and the clinical course of WM patients are heterogeneous, indeed. On one hand, at least 25% of patients with WM are asymptomatic at diagnosis, most of these patients will not require therapy [1] and they will be mainly at risk of unrelated death during the first 3 years. On the other hands, median overall survival (OS) ranged from 60 to 77 months in patients who received single agent regimen [2]. Overall, unrelated deaths and progression of WM with cytopenias, symptoms related to marrow failure or transformation to high-grade lymphoma are the main causes of death. Second malignancy and infection were the causes of 31% and 19% of deaths recorded in a Spanish series, respectively [3].

Because of the indolent course of the disease, the advanced age of a large subset of patients and the presence of competing causes of death unrelated to the disease, disease-specific survival has been considered an appropriate endpoint for assessing the respective effects of concomitant disorders and WM on life expectancy. Median disease-specific survival has been estimated as close to 11 years, confirming the indolent nature of the disease [4].

However, survival studies often have to deal with two important challenges: (i) separating effects of predictions on different 'competing' events and (ii) uncertainty about cause of death [5]. The definition of related and unrelated causes of death may be unsettled for many elderly patients (16%) because of the various disease-related complications that may occur during the course of the disease [6]: An increased risk of hematological malignancies (acute myelogenous leukemia or lymphoma) after purine analog exposure has been observed by some authors, but not others. Although, infection are very common in elderly patients, it remains difficult to rule out the role of the immunological abnormalities frequently observed in patients with WM. Therefore, models using the general population mortality such as net survival estimates, that would be observed if cancer was the only cause of death, are appropriate to express the effect of the disease and to compare cancer mortality between areas or countries. Models including competing events may also

more accurately address the effects of the progression of the disease, the occurrence of specific complications or unrelated causes of deaths.

In conclusion, disease specific survival is a simple way to take into account the competing causes of deaths, but the accurate identification of causes of death is the main drawback. Net survival or competing risk models provide more accurate information for better understanding overall survival estimates.

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