The importance of clinical endpoints in lymphoma

Lymphomas, or neoplasms of the lymphoid system, include a broad array of cancers. The least aggressive, often called indolent, lymphomas (the most frequent of which is follicular lymphoma, FL) are characterized by their incurability. At the same time, due to their slow growth and with the therapeutic improvements, some patients with FL can expect to live as long as the general population. Therefore, treatment needs to combine a care for the immediate disease control with the consideration of long term consequences and toxicities of therapy. One of the management options of these slow-growing disorders is that of not administering treatment at diagnosis, a strategy known as watchful waiting (WW). This is only possible in patients with low tumor burden, defined as the absence of symptoms (night sweats, fever or weight loss), organ damage or large tumor masses.

When treatment is required, there are a wide variety of drugs that are highly active against indolent lymphoma. However, contrary to what may seem intuitive, measuring the effectiveness of different treatment regimens, in order to compare them with one another, is complex, largely because no endpoint is devoid of shortcomings. The most important endpoint, overall survival (OS), the time from diagnosis to death of any cause, is hampered by the long time needed to assess it and the fact that the role of subsequent lines of therapy might prevent the proper assessment of any one of them specifically. Another one of the most commonly used endpoints, progression-free survival (PFS), the time from diagnosis until progression or death of any cause, has the problem that progression is not clinically relevant by itself since a patient can live treatment-free with progressive disease for years, if slow-growing and asymptomatic. Therefore, all endpoints have shortcomings that need to be kept in mind when assessing any therapeutic strategy and, particularly, when comparing them to one another. Indeed, only the combination of several endpoints can fully show the results of any treatment.

In a recent letter to the editor in the *British Journal of Haematology* we argue, as others have before, that PFS is particularly ill-suited to compare WW to any active treatment. This is because patients receiving any treatment will almost certainly have a longer PFS than patients receiving no treatment (because any tumor burden, as low as it may be, will, to some extent, be reduced by modern day therapy). However, patients following a WW strategy can still receive the same treatment whenever they actually progress and/or become symptomatic, thus benefiting from that treatment after the initial progression. We, therefore, praised the study by Nastoupil *et al* (in the same Journal) as well as a 2012 work by Solal-Celigny *et al* in the *Journal of Clinical Oncology*, because they specifically employed endpoints that seemed to more fairly compare WW with an active treatment. While different (the former used PFS from first active lymphoma treatment whereas the latter used freedom from treatment failure), they both took into consideration that WW is not so much another ‘line of therapy’ as it is a ‘delay of one.’

At present, we have at our disposal several highly active anti-lymphoma agents. Alongside the improvements in supportive care, this has led to a notable increase in the expected survival of

patients with FL. However, the disease still seems incurable and all treatments are toxic and pose significant risks for the patient. Therefore, it is important to remain rigorous and not lose perspective as to what each management strategy offers. An essential step towards that end is to use the most appropriate endpoints for each study.

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