



The significance of progression-free survival as an endpoint in evaluating the therapeutic value of antineoplastic agents

J.A. Maroun MD

In the last decade, thanks to the development of new and effective cytotoxic and biologic agents, significant progress has been achieved in the treatment of various forms of cancer. These new treatments, consisting of novel combinations of compounds, have contributed to significant increases in progression-free survival (PFS) and overall survival (OS) for patients. Nowhere has this progress been more apparent than in the overall improved efficacy in the treatment of what were traditionally very resistant tumours—for example, metastatic colorectal cancer. The earlier fluoropyrimidine-based monotherapies were associated with a median survival of 12 months. However, the availability of new cytotoxic agents (oxaliplatin, irinotecan, and new biologic agents with anti-vascular endothelial growth factor and anti-epidermal growth factor receptor effects), coupled with the implementation of sequential doublet combination chemotherapies, has increased median OS in patients to more than 24 months. Similar advances have also been demonstrated in other traditionally resistant tumour sites such as renal cell carcinoma, malignant melanoma, and ovarian cancer.

Although a welcome development, the availability of multiple lines of therapy leading to an overall increase in survival has also led to new challenges in the evaluation of specific lines of therapy, particularly when those therapies are associated with crossover or contamination effects from other available therapies. Such occurrences are so frequent that the approval of new agents and combinations has also become more challenging to regulatory agencies, because it becomes more difficult to tease out survival benefits for any specific or individual line of therapy.

Continued reliance on OS as an endpoint therefore limits the ability to evaluate new therapies when multiple lines of treatment are available to the patient and are regularly offered as therapy. The lack of consensus surrounding new antineoplastic therapies centres on the question of which endpoints are appropriate and valid in evaluating new treatments. The retention of OS, considered the “gold standard,” as the primary endpoint for the evaluation of therapies has led, in many cases, to an inability to assess certain drugs for approval, difficulties in establishing new standards

of care and evidence-based clinical guidelines, and delays in the approval of effective new therapies. In the meantime, failure to approve valuable new compounds in a timely fashion may result in suboptimal treatment for cancer patients.

To address those issues, leading Canadian and international clinicians, statisticians, and researchers participated in several workshops to discuss the most appropriate endpoints for the evaluation of each line of therapy. The participants discussed the value of PFS as a valid and realistic endpoint for tumour sites in which they are experts. Those workshops led to PFS being identified to be as realistic an endpoint as the “gold standard” OS. The proceedings of three workshops, organized under the auspices of the Canadian Oncology Societies (COS) and the Canadian Association of Medical Oncologists (CAMO) in cooperation with the Canadian Urological Oncology Group (CUOG) and with members of the Society of Gynecologic Oncologists of Canada, are published herein, thus providing a Canadian perspective to this important ongoing debate.

The separate issue of whether PFS can be accepted as a surrogate for OS was also discussed. However, that question has its own challenges because of the confounding effects of having to rely on older clinical trials with drugs that do not reflect current standard practice and of having to deal with variations in the statistical interpretation of the data. Despite those limitations, most experts believed that PFS could be a surrogate for OS. However, it is important to emphasize that, even if PFS is considered a relevant and valid endpoint, its implementation requires rigorous application criteria as outlined in the discussions.

In the articles that follow, PFS is discussed in relation to three tumour sites: colorectal cancer, renal cell carcinoma, and ovarian cancer. Further discussions are ongoing in lung cancer, malignant melanoma, and neuroendocrine tumours, which have traditionally been resistant to therapy. The use of PFS as an evaluation endpoint is contributing to a demonstration of the effectiveness of several compounds. We hope that publication of this Canadian perspective on the relevance of PFS as a valid endpoint in therapy

at specific tumour sites will initiate further debate between experts and regulatory agencies, and will result in resolution of the pertinent issues. Ultimately, recognition of PFS as an endpoint by regulatory agencies and experts could have a significant impact on

the welfare of cancer patients by providing earlier access to new and effective therapies.

We hope that the overview provided here will act as a stimulus to this emerging debate. We welcome your views and comments on this important discussion.