Progression-Free Survival Versus Overall Survival as the Primary End Point in Anticancer Drug Trials: Increasingly Relevant Impact of Therapy Following Progression

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There has been ongoing (and often highly contentious) debate regarding the appropriate primary end point in randomized trials of anticancer therapy [1,2]. The discussion centers on the important question of whether a statistically significant improvement in progression-free survival (PFS), in the absence of an ultimately proven favorable impact on overall survival, is a valid indicator of clinical benefit for a particular investigational strategy.

Another way to phrase the issue is to inquire if the only acceptable justification for delivering an anticancer therapy should be to delay the date of death, versus prolonging the time a patient may live without progression of objective signs or subjective symptoms of the malignancy in the absence of evidence for an improvement in overall survival.

Compounding this complex discussion is the fact that in an increasing number of cancers, there are "second-line" drug strategies that can have a favorable impact on survival following documented progression of a primary chemotherapy management program. Thus, a further question to be asked is whether an antineoplastic drug regimen administered in a clinical trial as initial therapy should be required to improve overall survival when treatment delivered following that regimen may substantially influence the patient's ultimate outcome, completely independent of the effect of the study program.

A relevant example of this complex issue is provided by data emanating from two well-designed and conducted randomized phase 3 trials in recurrent ovarian cancer [2,3]. One study compared a platinum-plus-taxane regimen with single-agent carboplatin [3]; the other compared carboplatin plus gemcitabine with single-agent carboplatin [2]. Both studies revealed a similar degree of relative PFS benefit (hazard ratios [HRs], 0.76 and 0.72) for the platinum-based combination [2,3].

However, although the "taxane" study demonstrated that the two-drug regimen was associated with an improvement in overall survival (HR, 0.82) [3], there was no difference in this parameter between the carboplatin-plus-gemcitabine program and single-agent carboplatin (HR, 0.96) [2]. One highly rational hypothesis to explain the rather surprising discordance between the outcomes of the two studies is that patients were managed quite differently following disease progression in the respective clinical trials.

Another example of this concern is the striking impact on overall survival (median improvement, 37 weeks) observed for recurrent (potentially "platinum-sensitive") ovarian cancer patients who were randomly assigned to the "liposomal doxorubicin" arm versus the "topotecan" arm in a randomized phase 3 trial directly comparing the single agents, when the actual difference in PFS (median improvement, 5.6 weeks) between the two study regimens was quite small [4]. Again, it is reasonable to speculate that the observation results from differences in how patients in the two investigative regimens were managed following progression. Specifically, it is rational to theorize that a greater proportion of women initially receiving treatment on the "less bone marrow–suppressive" liposomal doxorubicin arm could subsequently undergo a clinically meaningful attempt at retreatment with a biologically active carboplatin-based program, compared with those randomly assigned to the "more bone marrow–suppressive" topotecan program [4].

Unfortunately, in these studies, potentially highly relevant, detailed information related to how individuals were treated following their removal from (or completion of) the trial is not available. However, the results of a recently reported phase 3 trial examining the utility of pemetrexed in previously treated patients with malignant pleural mesothelioma provide strong support for the potential importance of therapy following progression in influencing overall survival among study participants [4]. The trial, which directly compared active single-agent pemetrexed plus "best supportive care" (BSC) with BSC alone, revealed a highly statistically significant improvement in several clinically relevant variables, including "disease control rate" (59.3% vs 19.2%; $P < 0.0001$), in favor of active treatment [5]. However, there was no difference in median overall survival between the study arms ($P = 0.74$).

Most relevant in the context of the current discussion were detailed, prospectively collected data regarding management after stopping trial-based treatment. Patients who were randomly assigned to the BSC-only arm were far more likely than those in the active treatment program to receive pemetrexed (18.3% vs 3.3%; $P = 0.0001$) after discontinuing the study regimen. Overall, 51.7% of patients in the BSC-only arm received at least one subsequent chemotherapy program compared with only 28.5% of individuals randomly assigned to receive pemetrexed ($P = 0.0002$). The posttrial therapeutic program also was administered much earlier in the BSC-only patient population (median, 4.3 vs 15.7 months after study initiation; $P < 0.0001$) [5].

In conclusion, although the quantity of existing evidence-based data certainly do not permit a definitive statement to be made regarding the potential impact of "therapy after trial completion" on a study population's ultimate survival, it is appropriate to raise the legitimate concern that highly clinically meaningful benefits of a new management strategy may be obscured or ignored by an understandable (but excessive) focus on overall survival as the primary (or only acceptable) end point.

Disclosure

No potential conflict of interest relevant to this article was reported.

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