which showed higher overall survival with combination treatment of docetaxel, estramustine, and prednisone than with combination treatment of mitoxantrone and prednisone, the historic standard palliative regimen for this disease (3). However, the combination regimen of docetaxel, estramustine, and prednisone produced only a modest survival benefit that was similar in magnitude to the benefit observed with docetaxel and prednisone alone in the multicenter TAX327 study (2). The additional cardiovascular, thrombotic, and gastrointestinal toxic effects associated with estramustine treatment have led to the conclusion that this agent likely has a minimal, if any, additive benefit in the first-line treatment of patients with metastatic castration-resistant prostate cancer. This assessment has been confirmed in a subsequent smaller randomized trial that evaluated treatment with docetaxel, estramustine, and prednisone vs that with docetaxel and prednisone alone, which showed no clinically significant differences in patient outcomes (4).

It is against this historic backdrop that the regimens in this phase II trial must be assessed (1). Because there was no docetaxel single-agent comparator arm in the study by Thall et al. (1), it is difficult to judge the merits of this aggressive and toxic approach. The authors claim that the rates for “overall success” and 5-year survival of 10% in their study justify this approach and that, in TAX327, no survival was observed beyond 48 months. However, this statement was not accurate, given that survival beyond 48 months was reported in the recently updated analysis of this trial was observed in 4.1% of patients in the every 3-week docetaxel and prednisone arm; only 1.5% of patients treated with mitoxantrone and prednisone survived beyond 4 years (5). A nomogram derived from the TAX327 trial may allow one to predict long-term survival by use of known baseline prognostic factors (6). Although nomograms may enhance our ability to predict 1-, 2-, and 5-year survival probabilities, routine use of such instruments in this context to evaluate the results of other trials still requires validation in carefully conducted prospective randomized trials.

Reliance on prostate-specific antigen (PSA)–based outcomes and other “response parameters” in the sequential randomized design may be a limitation of this design. Indeed, the use of non-standardized measures of PSA declines reported by Thall et al. (1) are difficult to assess because of the lack of supportive data on the surrogate value of these intermediate outcomes for the prediction of survival in patients with castration-resistant prostate cancer (7). More information on baseline prognostic characteristics of the patients, such as volume or burden of disease and known prognostic factors, should be reported, with particular emphasis on those characteristics associated with better survival. This data would allow a more rigorous assessment of the merits of the intensive regimens used in the study by Thall et al. (1). Finally, a description of the rates of progression-free survival, time to progression, and overall survival for each of the initial chemotherapy regimens would provide useful comparative data against currently approved therapies. Given that the median time to progression for the overall cohort was short at 4.9 months, selection bias may have played a relatively strong role in the favorable long-term outcomes in this trial.

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References


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Response
Armstrong et al. correctly point out that we made no comparison to the accepted standard therapy for symptomatic castration-resistant prostate cancer (namely, docetaxel and prednisone every 3 weeks). The purpose of our study was to evaluate the feasibility of a method for efficiently ranking, by order of clinical efficacy, four regimens widely used at the time that our study was designed. Importantly, we did this by means of a clinically grounded algorithm that also serves each individual patient. We believe our experience demonstrates that the method does efficiently rank order the regimens. In particular, the observation that the carboplatin-containing regimen fared better than others was unexpected for us, given carboplatin’s lack of efficacy as a single agent. This finding is in line with other recent reports and supports the validity of our approach.

The suggestion that incorporation of patients without metastatic disease or with other markedly favorable prognostic features could account for the observed survival is an important consideration for placing our results in context. Actually, there were five patients (3% of all 150 patients) in our trial with locally advanced disease (including invasion of bladder and invasion into pelvic sidewall) but without clinically detectable metastases. These five patients had survival times ranging from 10.9 to 38.5 months (median = 22.4 months), which is remarkably representative of all patients treated. By contrast, the notion that optimizing treatment strategy may contribute to improved survival is supported by the results of applying the prognostic model of Armstrong et al. (1) to the 145 patients with metastatic disease in our dataset (Figure 1). As shown, there was an apparently favorable survival of patients in our trial compared with the predicted survival that was based on the fitted model of Armstrong et al. (1) if the patients had received docetaxel every 3 weeks. As with all comparisons of results from separate trials, however, this comparison suffers from confounding of between-trial effects. We make no claim that any regimens that we used are superior to docetaxel or, indeed, that outcomes observed on our trial are superior to those in TAX327. Rather, we claim only that we treated patients with rather typical prognostic features and that our approach did not produce an obviously inferior patient outcome, despite the concerns expressed about the toxicity of the regimens we studied. We concur with Armstrong et al. (1) that the toxicity of estramustine adds urgency to the question of its contribution to any combination therapy.

Cancer treatment for an individual patient usually consists not of a single regimen but rather of sequentially applied regimens. Although this is routine in actual oncology practice, nearly all clinical trial designs, and most analyses, ignore this fact. Accounting for the sequential nature of most actual therapy is important because there may be carryover effects of first-line treatment on outcomes observed after second-line treatment. Our aim was to address these issues in a prospective trial that used an algorithm that reflects how oncologists practice. We previously published a detailed description (2) of the design’s properties and operating characteristics, demonstrating that indeed this design provides substantial probabilities of correctly selecting more active regimens. Although we have offered only one approach, we believe that Armstrong, Garrett-Mayer, and Eisenberger would agree that an objective method for selecting the most promising regimens for time-consuming and expensive phase III evaluation would be a substantial improvement over the current, largely subjective approach. Our findings, which require further confirmation, suggest that not only improvement in short-term outcomes that provide a basis for selection but also improvement in patient survival can be achieved by optimizing the treatment strategy.

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References


Notes

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