Reply to G. Sonpavde et al

Sonpavde et al1 raise a number of interesting points in their commentary concerning prognostic factors, treatment issues (cisplatin vs carboplatin), and trial design in urothelial cancer (UC) patients. The subject of their correspondence was the publication of the phase II data from the randomized European Organisation for Research and Treatment of Cancer (EORTC) Study 30986, which assessed gemcitabine/carboplatin and carboplatin/methotrexate/vinblastine in patients with advanced UC who were not eligible (“unfit”) for cisplatin-based chemotherapy.2 We know from the literature3 and daily clinical routine that the number of patients eligible for cisplatin-based standard chemotherapy for perioperative as well as advanced and metastatic disease is decreasing, representing < 50% of patients. On this point, we do agree completely with Sonpavde et al. Moreover, the value of our conducting the first randomized phase II/III study in a clear-cut and well-defined population of patients who were ineligible for cisplatin is reconfirmed by this commentary. In our study, only patients with performance status (PS) 2 and/or impaired renal function were allowed (preplanned stratification parameters) to be included in the trial.

So far, no standard chemotherapy has been established for this patient group. The phase III data from this pivotal study will be submitted for presentation at the American Society of Clinical Oncology 2010 Annual Meeting and might establish, to our knowledge for the first time, such a treatment standard. In addition, in this trial, valuable information about this specific patient group was collected and analyzed and will provide reference figures for progression-free survival (PFS) and overall survival (OS).

The question of whether renal dysfunction is an adverse prognostic factor by itself or if just the inability to administer cisplatin has an adverse impact on outcome, so far, has not been explored systematically. Some data about the impact of renal function as a prognostic factor are emerging from the second-line vinflunine trial performed in the United States and reported in a recent issue of Journal of Clinical Oncology.4 Our publication includes a post hoc analysis of results according to Bajorin’s prognostic groups,5 showing an excellent over-80%, and no visceral metastases, who qualified for the study only because of renal function impairment. These findings suggest that renal insufficiency has the least adverse impact on outcome compared with a lowered PS and/or the presence of visceral metastases. However, these post hoc findings are only hypothesis generating, and further investigation and validation in respective study cohorts is still needed and should be addressed in future studies and trial designs. The phase III data from our study will provide more insight into the patient subgroups with impaired renal function and good PS.

As is true for patients eligible for cisplatin in the first-line setting,6-7 PS and metastatic disease location have also been shown to be the most important clinical pretreatment prognostic factors for survival in patients at relapse after a platinum-containing regimen.8 In addition, in this patient cohort, a low hemoglobin level was a statistically significant predictor for a shorter OS at multivariate analysis, independent of the treatment arm.4 The first hint so far about renal function being an independent pretreatment prognostic factor in patients at relapse after platinum-containing chemotherapy was detected in the external validation set of the Vaughn trial,9 but not in the primary phase III trial cohort of this analysis, which might be explained by the different inclusion criteria of the respective studies (patients with slight impairment in renal function were allowed to be included in the Vaughn trial but not in the phase III study).

The question of whether carboplatin might be as effective as, but less toxic than, cisplatin combination chemotherapy in patients eligible for cisplatin has, so far, not been answered sufficiently. To date, no adequately powered phase III data have been generated. Several smaller studies on newer, non–cisplatin-containing triplets, dose-dense sequential therapy, and novel treatment options have shown promising response rates, including complete responses, as outlined in the commentary. High response rates in UC, however, do not necessarily correlate with a gain in PFS or OS. Until otherwise proven, we should be cautious about not using evidence-based treatment approaches in patients eligible for cisplatin. We might deprive these patients of a more substantial survival benefit and, above all, of a small, but realistic chance of long-term survival,7,10 which so far has not been shown with non–cisplatin-containing chemotherapy. In view of the available evidence and well-designed randomized trials, we strongly support the use of cisplatin combination chemotherapy in eligible patients. A patient’s and/or physician’s choice, just for convenience in daily clinical practice, is not what the oncologic community is recommending.

The last point addressed by the authors1 is a proposal for novel trial designs and use of end points in UC. The background for their concerns seems to be severe accrual difficulties in UC trials. To facilitate patient inclusion in clinical trials, Sonpavde et al propose to include cisplatin-eligible and cisplatin-ineligible patients with PS 0 to 1 in the same trial after stratification for cisplatin eligibility and to substitute carboplatin for cisplatin in the cisplatin-ineligible patients. However, because we still want to draw separate conclusions for these two groups, this concept does not help to reduce patient numbers, and the study would be underpowered to detect possible interactions. In addition, the question asked may be different in these two groups. The only advantage of such an approach seems to be from an administrative point of view, since there would be one protocol instead of two. However, patients with PS 2 would still have to be studied separately.

We agree that a PFS end point, as suggested by Sonpavde et al, might be an appropriate and convenient end point. However, the design of new studies based on PFS requires accurate estimates of PFS in the patient population of interest from previous studies. In addition, adequate data from randomized phase III trials need to be available for all patient groups—in our case for cisplatin-eligible and -ineligible patients—showing a clear correlation with OS. So far, the
first PFS and OS data from our randomized phase II/III trial in patients not eligible for cisplatin have not yet been reported but will be presented soon.

As recently discussed in a letter raising similar suggestions,1,1 PFS is an acceptable end point in situations where there is an unmet medical need or there are subsequent active agents that could obscure the final outcome regarding survival (eg, in breast cancer). Of note, with a PFS end point, we still have the problem of clinical progression in patients who stop treatment and go off study before an objective assessment of progression can be made. If a central external review of progression is implemented, additional problems may arise if there is disagreement between the central review and the local evaluation. For PFS, ideally a double-blind study should be performed, which may or may not be feasible. Novel trial designs and new study proposals for UC are welcome. Whether they will promote patient accrual, as suggested by Sonpavde et al, remains to be seen.

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