Randomized phase III trials of second-line chemotherapy in patients with advanced bladder cancer: progress and pitfalls

Few randomized clinical trials have been conducted in first-line setting and even fewer in the second-line setting in advanced bladder cancer. Overall, patients’ impaired renal function, poor performance status (PS), advanced age and comorbidities have limited trial design and feasibility. In addition to the difficulty accruing patients on such trials, several methodological issues related to patient and disease heterogeneity have limited the interpretation of phase II and even phase III trials [1].

The second-line bladder cancer trial reported by Albers et al. [2] in the present issue of Annals of Oncology merits the attention for being the second randomized trial after the publication of the vinflunine phase III trial [3] and for providing new information in this area. Patients failing first-line chemotherapy were randomized to a short- or long-term gemcitabine and paclitaxel (GP) combination. Although it was described as a phase III study, due to its sample size, in reality it should be considered in the realm of a randomized phase II design.

Taken together these two trials provide several key concepts and definitions that need to be considered when designing new trials and interpreting results in the second-line setting. These include (i) the definition of second-line therapy; (ii) the analysis based on eligibility versus intention to treat (ITT); (iii) the need for clear definitions of primary refractory disease, acquired resistant disease and recurrent disease after treatment; (iv) the use of prognostic factors for proper stratification; (v) the value of rechallenging with agents already used in first-line therapy and (vi) the role of prolonged/maintenance treatment in second-line versus a predefined period.

The definition of second-line therapy: Eligibility criteria for second-line phase II trials have been variable and sometimes confusing, limiting the interpretation and comparison of outcomes across studies. Therefore, a strict definition of what is ‘second line’ is needed. In bladder cancer, progression within 6 months of prior chemotherapy in the perioperative setting constitutes an obvious poor prognostic group of patients compared with those progressing beyond 6 months. Thus, lumping these two different categories of patients together could easily add a selection bias. In fact, some authors have suggested that these should be enrolled as a separate stratum [4]. In that regard, Albers’ trial included patients failing perioperative chemotherapy with different disease-free intervals and patients failing first-line chemotherapy for metastatic disease; this might have added a selection bias. In fact, when both subgroups were compared, no statistically significant difference for both progression-free survival (PFS) and overall survival (OS) was observed. However, the limited number of patients in each subgroup, the inadequate balance and stratification in both trial arms precludes us from any definitive conclusions. Consequently, to clearly define the role of any therapeutic strategy in second line, eligibility criteria need to be more homogeneous.

The analysis based on eligibility versus ITT: Considerable numbers of patients included in second-line bladder cancer trials drop out early in the course of study treatment. The limited life expectancy of these patients and the number of comorbidities leads to less benefit from chemotherapy and a worse side-effect profile [5, 6]. In Albers’ trial, six patients were excluded from ITT analysis due to violation of entry criteria or lack of treatment documentation. The final analysis in the ‘ITT population’ was done excluding these six patients. Furthermore, 15 additional patients were not assessable for response to treatment (4 patients died before starting the treatment), totaling 21% of all patients on this trial not assessable with less than one cycle completed. Conversely, in the larger vinflunine trial, in the pre-planned eligible population analysis (n = 357), median OS was significantly longer for vinflunine plus best supportive care (BSC) compared with BSC alone. Only 2% in the vinflunine trial did not receive the allocated treatment in the vinflunine arm (n = 253).

Although the ITT analysis did not show a significant OS advantage for vinflunine + BSC arm, there was a significant improvement in response rate and median PFS. These scenarios give us a glimpse about the complexity of demographics when interpreting the results of these trials and supports the importance of presenting results for both eligibility and ITT. These small differences may make a dramatic difference in study interpretation.

The need for clear definitions of primary refractory disease, acquired resistant disease and recurrent disease after treatment: Although not previously defined in bladder cancer, chemorefractory and chemosensitive populations probably exist in second-line bladder cancer. In ovarian cancer, small-cell lung cancer and germ-cell tumors, this concept is well established [7]. With that in mind, it is important to point out that in this trial by Albers, there was an imbalance between the arms in terms of modality of first-line treatment. The authors found a positive correlation between duration of response to first-line chemotherapy and the duration of response to the second-line GP, with patients progressing after 18 months from first line having the best response on the second line. However, despite the fact that this positive correlation was found, they also observed that the outcomes (PFS and OS) of patients who...
had received prior adjuvant chemotherapy did not differ from patients who were previously treated with front-line chemotherapy for metastatic disease. These observations suggest that response to second-line treatment was independent of progression after adjuvant or primary inductive chemotherapy, suggesting that patients with progression after cystectomy and adjuvant treatment do not a priori present a more favorable subgroup. However, the time elapsed from adjuvant chemotherapy to relapse is not necessarily a ‘lack of progression’ but rather the time it takes for microscopic disease to become macroscopically evident. Although those are interesting observations, unfortunately they are difficult to interpret based on heterogeneity of the patient population and the limited number of the patients studied. These data can only be considered as hypothesis generating. In the vinflunine trial, the analysis of the patients progressing before or after 3 months did not show any difference in treatment outcome. Before definitive statements are made, we still need to carefully consider patient stratification to avoid imbalances in clinical trials.

The use of prognostic factors for proper stratification: Well-established prognostic models for first-line treated patients with combination chemotherapy with methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC), including the presence of visceral metastasis, elevated levels of alkaline phosphatase and poor PS as risk factors [8]. However, when both vinflunine and the German trial were designed, no prognostic factors were available for second-line patients, and this fact is probably responsible for confounding the results of second-line randomized clinical trials, which was evident in both trials. In the vinflunine trial, patients were only stratified by study site and refractoriness to previous platinum treatment. Retrospectively, an imbalance of 10% was noticed for PS favoring the control arm. Interestingly, a multivariate analysis using a Cox proportional hazards model adjusted for prespecified prognostic factors (including PS) showed that vinflunine reduced the risk of death by 23% compared with BSC alone. Additionally, the vinflunine trial generated important information about prognostic factors in second-line treatment that allow appropriate stratification for future second-line clinical trials. Three adverse risk factors (poor PS, hemoglobin level <10 g/dl and the presence of liver metastasis) were identified as predictors of OS and both internally and externally validated [9]. Along the same line, the German trial examines the effects of selected baseline prognostic factors on treatment response, confirming on the value of hepatic metastasis as a poor prognostic feature and lymph node only disease as a favorable prognostic feature.

The value of rechallenging with agents already used in first-line therapy: Retreatment with previously used agents is of unclear benefit in bladder cancer. Most second-line treatment trials were based on single-agent nonplatinum therapy. However, M-VAC second-line therapy might be considered appropriate in very fit patients with nonvisceral disease able to afford the potential risk of toxicity. Additionally, readministration of the same first-line chemotherapy regimen might be considered if the previous quality of response was excellent or the time to progression was long (i.e. >12 months); limited data supporting this strategy exist for M-VAC [10]. In the Albers trial, ~50% of the population had received gemcitabine-based chemotherapy in the first line. This GP combination is synergistic in vitro at clinically achievable doses [11]. An interesting observation of the current trial is that gemcitabine pretreated patients had similar outcome in terms of OS and PFS when compared with gemcitabine-naive patients. The observed efficacy of the GP combination in gemcitabine pretreated patients seems to provide support to the idea that synergy may be achieved between the two agents. Additionally, the sequence of administration of paclitaxel and gemcitabine may be important. In a phase I/II study in patients with non-small-cell lung cancer, paclitaxel and gemcitabine did not affect each other’s pharmacokinetics, but paclitaxel administration before gemcitabine increased difluorodeoxycytidine triphosphate levels, the active metabolite of gemcitabine, suggesting that this sequence might enhance the antitumor activity of the combination [12].

The role of prolonged/maintenance treatment in second line versus a predefined period: In the current trial, it was not possible to demonstrate a superior OS or PFS of long- versus short-term GP in second-line treatment. However, the median number of cycles delivered for both treatment arms was not different. The authors conclude that prolonged treatment as maintenance therapy is not feasible (median number of 4 cycles), probably due to the patients’ poor prognosis. We believe that the concept of prolonged or maintenance in patients obtaining a clear benefit is an attractive strategy. What is clear is that drugs used in the maintenance strategy need to be both active against the cancer, highly tolerable and convenient for patients that may have experienced toxicity in front-line cisplatin-based chemotherapy. This type of approach is currently being explored using targeted agents in monotherapy or in combination with taxanes until progression [13, 14].

The experience gained in design and conduct of randomized trials in second-line bladder cancer will be helpful for future trials. While the activity of vinflunine is modest, responding patients did obtain prolonged benefit. In Europe, vinflunine forms the basis of future trial design in second line, while in the United States, no standard second-line regimen currently exists. The presence of externally validated clinically significant prognostic factors have now been identified for patient stratification for future trials. The current trial has also generated important information about the role of GP combination therapy, on treatment duration, the role of rechallenging with gemcitabine and in prognostic factors. Yet, there is much room for improvement in second-line treatment of bladder cancer. In the future, incorporation of novel biological agents into bladder cancer treatment may yield the most fruitful path forward. Future trial design will need to take in consideration the methodological issues learned from these two trials.

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disclosure

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references