Drs. Vaughn and Malkowicz have provided us with a succinct, thorough, evidence-based overview of the current role of chemotherapy in advanced bladder cancer. Their discussion highlights the veritable explosion of new chemotherapy agents with impressive activity in advanced urothelial cancer, the evidence against the routine administration of chemotherapy in the neoadjuvant setting, and in contrast, the paucity of data in the adjuvant setting. They also provide a look into the future with a brief review of evolving molecular prognostic factors.

Chemotherapy for Advanced Bladder Cancer

The M-VAC regimen (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin [Platinol]) is now over 15 years old. Its introduction into clinical practice in the 1980s represented the first significant development in the management of advanced urothelial cancer. M-VAC is clearly among the most toxic chemotherapy combinations in our armamentarium, and yet it has only a modest impact on survival (3.7% survival at 6 years’ median follow-up in the Intergroup study).[1] A large number of new chemotherapy agents introduced into clinical practice in the late 1980s and 1990s have demonstrated significant activity in advanced urothelial cancer. Phase II evaluations of paclitaxel (Taxol), gemcitabine (Gemzar), and ifosfamide (Ifex) as single agents and in combination with other active agents have demonstrated intriguing response rates with some suggestion of improved median survival.[2-4]

Significant activity of the gemcitabine/cisplatin (Platinol) combination in phase II trials led to an important industry-sponsored, multicenter, international phase III trial comparing gemcitabine/cisplatin to M-VAC.[5] This trial impressively accrued over 400 patients in 2 years, and while it was not powered as an equivalency trial, its results suggest that the gemcitabine/cisplatin combination is a viable alternative to M-VAC. However, one must not lose sight of the fact that the median survival in the gemcitabine/cisplatin arm was 13.8 months, compared with 14.8 months for M-VAC, suggesting that real progress has not yet been achieved.

One of the most challenging aspects of our current surplus of active chemotherapy agents is the increasingly competitive environment in which phase II trials are performed. An even greater task is the selection of optimal regimens to take into phase III studies. This quandary exists due to the limited number of available patients (approximately 12,000 new advanced bladder cancer diagnoses each year in the United States, with less than 3% enrolling in clinical trials).[6] The traditional method of basing optimal regimens for phase III studies on comparisons of overall response rates in phase II studies is problematic in urothelial cancer, because the vast majority of trials report response rates with overlapping confidence intervals.

Another confounding issue is the distribution of patients with known poor prognostic features (eg, poor performance status, visceral metastatic disease, renal insufficiency) that can negatively affect response rates, resulting in a clinically relevant bias when compared across various phase II studies. Drs. Vaughn and Malkowicz refer to recent work by Bajorin et al, in which a method of quantitating these risk factors can be applied across phase II studies in an attempt to control for known prognostic factors in urothelial cancer.[7]
A myriad of important questions remain unanswered. The relative role of carboplatin (Paraplatin) vs cisplatin in urothelial cancer remains unclear. Although there are suggestions that cisplatin is superior, no studies have formally addressed this controversy to date. Other issues include the utility of two- vs three-drug combinations. This question will be addressed by the proposed European Organization of Research and Treatment of Cancer/Southwest Oncology Group phase III trial comparing gemcitabine/cisplatin vs gemcitabine/cisplatin/paclitaxel.

Cisplatin-based regimens are typically contraindicated in patients with renal insufficiency, who represent 10% to 20% of patients with advanced bladder cancer, and as such, present a significant therapeutic dilemma to clinicians. Dr. Vaughn has taken a leadership role in this area by directing a series of Eastern Cooperative Oncology Group phase II trials of nephron-sparing combinations (E2896, carboplatin/paclitaxel; E5899, gemcitabine/paclitaxel) in this subset of patients. These trials may demonstrate the utility of therapy, albeit with a lower response rate.

Conclusions

Although clinicians who treat patients with advanced urothelial cancer today have an ever-increasing armamentarium from which to choose, there remains no compelling evidence that significant progress has been made. Many liken our current state of therapeutics in advanced urothelial cancer to that of small-cell lung cancer in the early 1990s, with high response rates but limited impact on overall survival. Drs. Vaughn and Malkowicz’s discussion of prognostic biomarkers highlights the current drive to develop biologically based treatment strategies.

Perhaps the most pressing issue before us today is to select specific agents from a host of novel small molecules (eg, farnesyl transferase inhibitors, proteosome inhibitors) for clinical trials in advanced urothelial cancer. Additional challenges will follow, as the integration of these novel agents into established chemotherapy regimens will likely require phase III designs to determine the relative benefit of these new molecules.

References:


