Potential Role of Vinflunine in Two-tiered Treatment Strategies – Perioperative and Maintenance Therapy

Fabio Calabrò

Department of Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy

The potential role of vinflunine in sequential treatment strategies for urothelial carcinoma, in both the perioperative setting and maintenance therapy, will be highlighted below.

Rationale for Perioperative Systematic Therapy in Bladder Cancer

The natural history and evolution of urothelial carcinoma suggests that the study of perioperative systemic therapy may yield benefits (see *Table 1*),[1–9] because 20–50 % of patients experience distant recurrence, and 5–15 % have locoregional recurrence.

The gold standard for patients with muscle-infiltrating disease is cystectomy. However, when comparing cystectomy series, survival is strictly related to the invasion of the bladder wall (see *Table 1*). The probability of non-recurring and organ-confined disease is approximately 80–90 %, while in patients with extravesical invasion it drops to 60 % and to 30 % in patients with nodal involvement after cystectomy. These figures explain why perioperative chemotherapy is an attractive option. Based on good responses obtained in advanced disease, chemotherapy is shifting to the neoadjuvant setting.

Long-term results of radical cystectomy in the treatment of invasive bladder cancer were presented by Stein et al. in 1,054 patients. Increasing tumour stage and nodal involvement were associated with significantly higher recurrence rates and worse overall survival (OS) (p<0.001). Specifically, patients with extravesical disease or lymph node positive (LN+) disease had a higher risk of recurrence compared with patients who had organ-confined disease. The 10-year OS for patients with extravesical bladder tumours was 27 %. In patients with LN+ disease the OS at 10 years was 23 %. Respective recurrence-free values were 47 % and 31 %.[5] These data provide a strong biological rationale for perioperative systemic therapy in bladder cancer.

Neoadjuvant or Adjuvant Therapy in Invasive Bladder Cancer

Several unanswered questions arise when gauging perioperative treatment options and the timing of cystectomy in patients with invasive bladder cancer. For instance, should radical cystectomy be performed without delay or is neoadjuvant chemotherapy a valid strategy? Should cystectomy be performed regardless of chemotherapy? Should the bladder be preserved and cystectomy be delayed according to chemotherapeutic response? Should adjuvant chemotherapy be administered, and if so, which regimen would be the most suitable?

Neoadjuvant Chemotherapy

Based on the encouraging results obtained with cisplatin combination chemotherapy regimens in patients with advanced, metastatic disease, use of neoadjuvant chemotherapy has been advocated to improve survival in patients with micrometastatic disease, and second, to preserve the bladder. It is thought that therapy may be better tolerated in patients upfront prior to cystectomy. On the other hand, neoadjuvant chemotherapy may make surgery more challenging and increase post-operative complications. A malignancy that is resistant to neoadjuvant chemotherapy may progress due to delay of surgery. Other disadvantages associated with neoadjuvant chemotherapy include difficulties in assessing response, and the fact that staging is based on clinical rather than pathological criteria. Benefits obtained in some studies are not reproducible. Only meta-analyses allowed to show a survival benefit ranging from 5 to 7 % (see *Table 2*).

Almost all neoadjuvant chemotherapy trials were negative, except for that conducted by the Southwest Oncology Group (SWOG) in 317 patients, which compared methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) followed by cystectomy versus cystectomy alone. The median survival for patients treated with neoadjuvant MVAC was 77 months compared with 46 months in patients treated with cystectomy alone (p=0.06). Respective 5-year survival was 57 % versus 43 %. The results achieved borderline statistical significance due to a long accrual and follow-up period. Patients treated with surgery alone had a 33 % greater risk of death compared with those treated with combination therapy (hazard ration [HR]=1.33, 95 % confidence interval [CI] 1.00 to 1.76).[8] These data strongly support the argument that neoadjuvant chemotherapy followed by radical cystectomy should be further investigated as an approach to optimise muscle-invasive bladder cancer treatment.

A subsequent retrospective analysis showed that patients who underwent neoadjuvant chemotherapy and successful surgery, having had more than 10 lymph nodes removed, had a 5-year survival of 81 %, whereas patients who did not receive neoadjuvant chemotherapy and had fewer than 10 lymph nodes removed had a 5-year survival of 39 %.[15] Surgical factors, therefore, have a considerable impact on bladder cancer outcome, and many factors are determinant for survival (see *Table 3*). The quality of surgery cannot be underestimated.

The largest neoadjuvant chemotherapy randomised trial was performed in 976 patients with T2–T4 muscle-invasive N0 urothelial cancer.[10] Patients were randomised to three cycles of cisplatin, methotrexate and vinblastine (CMV) versus no CMV, followed by either cystectomy or radiotherapy local treatment that was left to the investigator's discretion. When first published in 1999,[16] the data did not reach statistical significance, but at 7 years of follow-up, a 6 % survival difference in favour of patients treated with neoadjuvant CMV was reported, and the results reached borderline significance (HR=0.85, 95 % CI 0.72–1.00; p=0.048).[11] With a longer follow-up of 10 years (median follow up of 8

years), the 6 % survival difference was maintained with neoadjuvant CMV (HR=0.84, 95 % CI 0.72–0.99; p=0.037).[17]

Meta-analyses have been performed, notably by the Advanced Bladder Cancer (ABC) collaboration group.[18] Evaluation of 11 randomised neoadjuvant chemotherapy trials, including a total of 3,005 patients, showed that the subgroup of patients treated with a cisplatin-based combination could benefit from an approximately 5 % absolute survival advantage at 5 years. One point of interest is the definition of the optimal endpoint of neoadjuvant chemotherapy. Studies and experience show that patients who obtain a pathological complete response (pCR) after neoadjuvant chemotherapy have a better outcome compared with patients who are not downstaged, or to patients with nodal involvement.[19]

The threshold for absolute difference in survival is a point of debate. A difference of 10 % has been proposed as a minimal threshold for success,[17] which may arbitrarily obscure the benefit conferred by perioperative chemotherapy. Colon cancer literature has, for instance, shown that adjuvant chemotherapy demonstrated a survival improvement with smaller absolute survival differences.[20] Another concern is that many patients are ineligible for cisplatin-based combination adjuvant chemotherapy. There is a concern that toxicity of neoadjuvant chemotherapy could delay surgery, although data from the Medical Research Council/European Organisation for Research and Treatment of Cancer (MRC/EORTC) and SWOG studies suggest that this is not the case.[8,17]

Patients with small pT2 tumours can be cured with surgery alone, and it has been proposed that it may not be in their interest to receive neoadjuvant treatment. Survival data from the SWOG trial argue against this notion,[8] as neoadjuvant chemotherapy-prolonged patient survival with clinical T2 tumours by 2.5 years compared with surgery alone. Furthermore, surgical clinical staging data have shown that low-risk clinical T2 patients who can be spared chemotherapy cannot be accurately identified by urologists.[21–23]

It has also been argued that patients could receive adjuvant chemotherapy instead of neoadjuvant chemotherapy with a similar survival benefit. Although plausible, in practice, a third of patients do not receive postoperative chemotherapy following cystectomy, mainly because of poor PS, complications related to surgery, psychological distress, age or patient refusal. Quality of life data would help address the question of whether neoadjuvant therapy may be preferable to adjuvant therapy.

Adjuvant Chemotherapy

The perceived benefits and detriments of adjuvant chemotherapy have also been the centre of debate. The advantages of adjuvant chemotherapy include accurate pathological staging, which facilitates evaluation of patient risk. Chemotherapy can be avoided in low-risk patients, and overtreatment can thus be prevented. Finally, this practice avoids delaying definitive surgery. The main disadvantages are that no *in vivo* assessment of patients is available, and that many patients are less able to tolerate chemotherapy after surgery.

An ABC meta-analysis showed an absolute survival benefit of 9 % (HR=0.75, 95 % CI 1–16 %; p=0.019) at 3 years in patients who received cisplatin-based therapy, although these data are likely flawed by the poor quality of the trials included.[24] Most adjuvant chemotherapy trials are underpowered, and have included fewer than 100 patients,

Table 1: Selected Cystectomy Series from 1991 to 2003

Reference	Year	Number	pT0	Mortality	pT2	pT3	pT4
Roehrborn et al.[1]	1991	280	–	2.1 %	63 %	36 %	24 %
Pagano et al.[2]	1991	261	9 %	1.8 %	57 %	15 %	21 %
Wishnow et al.[3]	1992	188	5 %	1.1 %	79 %	46 %	33 %
Waehre et al.[4]	1993	227	25 %	–	61 %	36 %	29 %
Vieweg et al.[5]	1999	686	–	–	58 %	22 %	15 %
Stein et al.[6]	2001	633	6 %	3 %	72 %	48 %	33 %
Dalbagni et al.[7]	2001	284	10.7 %	–	59 %	25 %	29 %
Madersbacher et al.[8]	2003	507	–	4.5 %	74 %	52 %	36 %
Grossman et al.[9]	2003	154	15 %	0.6 %	75 %	–	24 %
Total		3,220	12 %	2.2 %	66 %	35 %	27 %

Table 2: Selected Neoadjuvant Chemotherapy Randomised Trials Performed in the 1990s

Reference	Investigational Arm	Standard Arm	Number	Survival Benefit
MRC/EORTC[10]	CMV RT/RC	RT/RC	976	No difference
Nordic 1[11]	CDDP-ADM+RT/RC	RT/RC	311	15 % in T3/T4a
Nordic 2[12]	MTX-CDDP+RC	RC	317	No difference
GUONE[13]	MVAC+RC	RC	206	No difference
MD Anderson[14]	MVAC RC MVAC	RC MVAC	140	No difference
Grossman et al.[9]	MVAC RC	RC	317	Yes

ADM = adriamycin; CDDP = cisplatin; CMV = cisplatin, methotrexate, and vinblastine; MRC/EORTC = Medical Research Council/European Organisation for Research and Treatment of Cancer; MVAC = methotrexate, vinblastine, doxorubicin and cisplatin; MTX = methotrexate; RC = radical cystectomy; RT = radiotherapy.

Table 3: Surgical Factors Impact on Survival in Bladder Cancer[10]

Variable	HR	95 % CI	p
MVAC+cystectomy versus cystectomy	1.0	0.7 to 1.4	0.97
Age ≥65 versus <65	1.5	1.0 to 3.6	0.03
pT 3–4 versus 0–2	2.3	1.5 to 3.6	0.0002
LN+ versus LN-	1.6	1.0 to 2.5	0.04
Positive versus negative margins	2.7	1.5 to 4.9	0.0007
LN removed <10 versus ≥10	2.0	1.4 to 2.8	0.0001

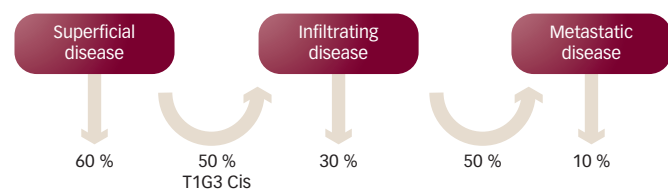| Variable	Five-year Survival	No Recurrence
MVAC neoadjuvant and ≥10 LN	81 %	91 %
Surgery ≥10 LN	64 %	90 %
MVAC neoadjuvant and <10 LN	55 %	66 %
Surgery <10 LN	39 %	66 %
Positive margins	0 %	0 %
No surgery	11 %	12 %

CI = confidence interval; HR = hazard ratio; LN = lymph node; MVAC = methotrexate, vinblastine, doxorubicin and cisplatin.

complicating the drawing of definite conclusions. Data exploring adjuvant chemotherapy have shown that many patients are ineligible for cisplatin-based combination adjuvant chemotherapy after surgery. Once again, the quality of received surgery is essential to optimise patient prognosis. Three recent trials have closed due to poor accrual. Data from a prospective meta-analysis of the EORTC individual patient data will be of interest.

How can Perioperative Chemotherapy Results be Improved?

Suggestions on how to improve outcomes of perioperative chemotherapy include the discovery and use of predictive factors of response, and the use of new drugs and targeted agents.

Urothelial Carcinoma

Figure 1: The Natural History and Evolution of Urothelial Carcinoma

| Superficial disease | | Infiltrating disease | | Metastatic disease |

60 % 50 % 30 % 50 % 10 %
T1G3 Cis

Cis = carcinoma in situ.

Table 4: New Triplet Chemotherapy Combinations with Paclitaxel

Reference	Regimen	Number	Median OS	CR	PR	RR
Bellmunt et al.[33]	Gem-CDDP-Tax	58	15.8	28	50	78
Hussain et al.[34]	Gem-Carbo-Tax	47	14.7	32	36	68
Bajorin et al.[32]	Ifo-Tax-CDDP	44	20	23	45	68

Carbo = carboplatin; CDDP = cisplatin; Gem = gemcitabine; Ifo = ifosfamide; OS = overall survival; PR = partial response; RR = response rate; Tax = paclitaxel.

Table 5: New Triplets: Phase III Trials Evaluating Dose Intensity

Reference	Regimen	Number	RR	Median OS
Bellmunt et al.[35]	GC	314	43.6 %	12.7
	PGC	312	55.5 %	15.8
Sternberg et al.[36]	HD-MVAC	134	64 %	15.1
	MVAC	129	50 %	14.9
Bamias et al.[37]	DD-GC	57	47.4 %	18.4
	HD-MVAC	118	47.4 %	20.7

GC = gemcitabine plus cisplatin; DD = dose-dense; (HD)-MVAC = (high-dose) methotrexate, vinblastine, doxorubicin and cisplatin; OS = overall survival; PGC = paclitaxel, gemcitabine, cisplatin; RR = response rate.

Based on retrospective studies suggesting that urothelial carcinoma patients with altered p53 had worse survival compared with patients who had wild-type p53, a randomised trial evaluating MVAC adjuvant chemotherapy was performed in these patients after cystectomy.[25] Based on p53 status, 521 patients were randomised to receive MVAC for three cycles versus observation. The results of initial studies were not corroborated, and the predictive and prognostic value of p53 status was not confirmed.

The study and validation of predictive factors is likely to be among the most interesting fields in the development of new drugs, because tumour biopsies are available prior to chemotherapy. Studies can be performed before administering chemotherapy (e.g. genomics or proteomics). Following treatment and radical cystectomy, the mechanism of resistance can for instance be studied in patients with residual tumours who do not respond. pCR can be rapidly determined after surgery, or after three to four cycles of neoadjuvant chemotherapy. Given that pCR is a favourable prognostic factor correlating with long-term outcomes, the efficacy of a systemic regimen is evident early.

Vinflunine may be an interesting agent in this setting, because vinca alkaloids are active as single agents in bladder cancer, and they have been incorporated in most bladder cancer chemotherapy regimens (as vinblastine). A phase I/II study in 53 patients with advanced non-small cell lung cancer (NSCLC) demonstrated that the combination of vinflunine with cisplatin was safe, with doses of 80 mg/m^2 cisplatin and 320 mg/m^2 vinflunine. Pharmacokinetic analyses showed no interactions between these two drugs.[26] It may be helpful to develop a phase I/II feasibility trial of a dose-dense q3w (in order for patients to receive treatment on 1 day) neoadjuvant regimen with cisplatin plus vinflunine to see if it is tolerated in bladder cancer in the same way as in NSCLC, as bladder cancer patients are often more frail and perform worse than patients with other tumours.

There are thus two opportunities to incorporate vinflunine in new potential perioperative chemotherapy regimens. First, bladder cancer patients could be treated in the neoadjuvant setting with a combination of cisplatin and vinflunine. A phase II exploratory study would be interesting in this context, with inclusion of translational endpoints. The trial could, for example, be used to assess response rates and identify potential markers (akin to an *in vivo* chemosensitivity test), and then moved to a subsequent use of cisplatin plus vinflunine phase II randomised trial. Second, in patients who have been treated with a standard combination of cisplatin and gemcitabine, vinflunine could be used in patients who did not respond to treatment. These are situations for which the role of vinflunine has not been explored. The effect of vinflunine on the subsequent cystectomy and neobladder is for instance not known (e.g. hepatic and renal toxicity). However, MVAC neoadjuvant chemotherapy is currently used in all patients with muscle-infiltrating disease, so nephrotoxic and potentially hepatotoxic drugs are being delivered with no major complications. The trials outlined above demonstrate that noeadjuvant chemotherapy does not add toxicity to surgery. Over the last 10 years, the neoadjuvant therapy approach has become more popular, due to more convincing data. Resistance from both oncologists and urologists is receding. A recent survey in the US, however, reported that twice as many physicians administered adjuvant chemotherapy compared with neoadjuvant chemotherapy.[27] A phase III trial is planned in the neoadjuvant setting that is going to investigate cisplatin plus gemcitabine versus accelerated MVAC, with the objective of comparing regimens and collecting tissue samples to assess whether efficacy can be predicted. One of the caveats associated with performing this randomised trial is that both arms are experimental. Standard MVAC was initially planned, but accelerated MVAC was chosen because it is better tolerated and may be more active.[28]

Two-tiered Treatment Strategy in the Metastatic Setting

In the metastatic urothelial carcinoma setting, problems include the fact that it is an aggressive disease, which despite being chemosensible, has not been investigated in a large number of randomised controlled trials. Metastatic urothelial carcinoma affects an elderly population, and is associated with various comorbidities that include reduced renal function.

Von der Maase et al. compared GC versus MVAC in patients with locally advanced or metastatic TCCU (n=405). OS, time to progressive disease, time to treatment failure and response rate were similar in both arms. However, GC had a better safety and tolerability profile compared with MVAC,[29] which is why most trials use GC as the preferred chemotherapy template for patients with locally advanced and metastatic TCCU. The median survival of GC or MVAC regimens is about 15 months, although outcomes demonstrate heterogeneity based on the number of prognostic factors (PS <80 % and visceral metastases).[30,31]

Over that last 20 years, treatment objectives in metastatic urothelial carcinoma have been to increase the number of CR and prolong response duration. The therapeutic strategies that have been adopted include evaluation of new combinations (e.g. triplets), sequential therapies, maintenance therapies, new drugs and molecular targeted therapies.

New Combinations

In investigations of new triplet combinations, the addition of paclitaxel to GC did not demonstrate a statistical improvement in survival of urothelial carcinoma, nor did dose-dense chemotherapy regimens (see *Tables 4* and *5*).[32–37] Phase III randomised trials have not shown important improvements in OS when investigating regimens other than GC or MVAC (see *Table 6*).[29,36,38–43]

Thus, in the field of metastatic urothelial cancer treatment, a plateau has probably been reached, with little improvement in the last 10 years with doublet or triplet combinations. MVAC and GC regimens are firmly established as standard chemotherapies in the first-line setting, and vinflunine is the only approved drug for use after failure of a platinum-based regimen. The role of targeted therapies in the treatment of metastatic bladder cancer is still not known.

Sequential Therapies

Theoretical models suggest that sequential administration of chemotherapy may improve targeting of different cell populations within a tumour. Additionally, administration of two or three sequential drug combinations in high doses may overcome the toxicity associated with simultaneous administration of those agents. For instance, in a phase II trial conducted by Galsky et al., dose-dense doxorubicin plus gemcitabine followed by paclitaxel and carboplatin was given to 25 patients with advanced urothelial carcinoma and renal impairment.[44] Overall response rate was 56% (including 35 % CR) (95 % CI 35–76 %), and median OS was 15 months (95 % CI, 11–30 months). Myelosuppression was the major toxicity, with 28 % G3/4 neutropenia. The 3-year survival was 25 %, and 28 % of patients were disease-free at 45 months. Dose-dense sequential chemotherapy was therefore tolerable and active in these patients. Prolonged disease-free survival was achieved in a subset of patients with primary unresectable disease or LN+ disease treated with carboplatin-based therapy with or without surgery.[44]

Another example of sequential therapy was developed by Milowsky et al., who combined sequential doxorubicin plus gemcitabine and ifosfamide, paclitaxel and cisplatin chemotherapy in 60 patients with metastatic or locally advanced TCCU. The study reported an impressive 73 % response rate (RR), but the population included 77 % of patients with local disease, 57 % with no risk factors and surgery was performed in 22 % of patients. The median OS was 16.4 months (95 % CI 14.0–22.5 months). Grade 3/4 neutropenia was observed in 68 % of patients. The authors concluded that the regimen was active but associated with elevated toxicity, which did not appear to be superior to non-sequential regimens.[45]

An additional rationale for sequential therapy is that different cell types are present in a given population of tumour cells,[46] and clonal populations may develop when treated with a combination regimen. Administration of sequential therapy may slow the development of subclones.

Maintenance Therapy and Targeted Therapy

Based on vinflunine efficacy following failure of platinum-based chemotherapy,[47–49] maintenance therapy with vinflunine could be of interest. With the knowledge that resistance occurs over time,[50] the early use of non-cross-resistant treatment regimens could be interesting after first-line platinum-based chemotherapy, because this approach may increase the probability of killing more cancer cells before the development of resistance.

Table 6: Phase III Studies

Reference	Regimen	Number	RR	Median OS
Loehrer et al.[38]	MVAC	126	39	12.5
	CDDP	129	12	8.2
Logothetis et al.[39]	MVAC	65	65	12.6
	CISCA	55	45	10
von der Maase et al.[29]	MVAC	202	48	14.8
	GC	203	49	13.8
Sternberg et al.[36]	MVAC	134	62	14.5
	HD-MVAC	129	50	15.1
Bamias et al.[40]	MVAC	109	54	14.2
	DC	111	37	9.3
Dreicer et al.[41]*	MVAC	44	36	15.4
	PCa	41	28	13.8
Bellmunt et al.[42]	PGC	312	57	15.7
	GC	315	46	12.8
Bamias et al.[43]	DD-GC	57	47.4 %	18.4
	HD-MVAC	118	47.4 %	20.7

*Trial stopped early. CISCA = cisplatin, cyclophosphamide, doxorubicin; GC = gemcitabine plus cisplatin; DC = docetaxel and cisplatin; DD = dose-dense; (HD)-MVAC = (high-dose) methotrexate, vinblastine, doxorubicin and cisplatin; OS = overall survival; PCa = paclitaxel and carboplatin; PGC = paclitaxel, gemcitabine, cisplatin; RR = response rate.

Newer cytotoxic drugs and targeted therapies may be more effective than more traditional standard treatments. The former often have an improved tolerability profile, meaning that treatment can be extended for a longer period of time. Patients who have an objective response or disease stabilisation after initial chemotherapy may benefit from maintenance therapy when tumour burden is low. There are two methods of administering maintenance therapy. The first is continuation maintenance, which consists of using at least one of the agents given in the first-line setting line beyond four to six cycles, in the absence of disease progression. The second – probably more interesting – is switch maintenance, which involves the initiation of a different agent with a separate mechanism of action, not included as part of the first-line regimen, in the absence of disease progression, after four to six cycles of therapy.

Approved treatment algorithms for maintenance therapy have been developed in metastatic NSCLC. Whether to offer continuation maintenance, switch maintenance or a chemotherapy break to a patient who is responding after four cycles of first-line chemotherapy is a decision that must be made with the patient on an individual basis.[51] Patients are only candidates for maintenance (switch or continuation) if they have had a tumour response or have stable disease after four to six cycles of chemotherapy. Observation is also an option.[51]

In NSCLC, as shown in a recent single-agent meta-analysis of 12 studies in a total of 4,286 patients,[52] patients who had maintenance chemotherapy consistently performed better than patients who were followed by observation alone. Switch maintenance was also shown to be superior to continuation maintenance.[52] On the strength of these maintenance data in NSCLC, two maintenance studies have been initiated in fit TCCU patients not progressing on cisplatin-based chemotherapy. The international JASIMA multicentre in 77 patients will evaluate vinflunine maintenance after four cycles of GC combination. The second maintenance study is the randomised phase II multicentre MAJA Spanish trial in patients (39 per arm) who will be randomised to receive vinflunine+BSC versus BSC alone after six cycles of GC (NCT01529411). The primary objectives of these studies is PFS. Maintenance trials ought to be designed to measure time to disease progression, for which a randomised design is essential. The MAJA trial is a randomised trial.

There may be concerns with patient heterogeneity, because eligible patients were allowed to receive four to six GC treatment cycles prior to randomisation. However, it is an exploratory trial that will help assess the toxicity of switching to a different drug with a separate mechanism of action, and whether maintenance therapy with vinflunine provides some benefit in terms of relapse.

Conclusion

Neoadjuvant chemotherapy is an interesting potential approach in the development of new drugs, and may expedite the development of new agents. A feasibility study evaluating the combination of neoadjuvant cisplatin and vinflunine would be of interest in bladder cancer patients, and the inclusion of a translational component would add value to the analysis, in order to identify biomarkers. The study would naturally involve strict control of the primary tumour, because cystectomy will be delayed in participating subjects. Vinflunine may have a role as front-line neoadjuvant chemotherapy in combination with cisplatin or in non-responders after cystectomy. In addition to neoadjuvant chemotherapy, there is also a strong rationale for maintenance chemotherapy, and vinflunine may also play a role in this setting. ■

1. Roehrborn CG, Sagalowsky AI, Peters PC, Long-term patient survival after cystectomy for regional metastatic transitional cell carcinoma of the bladder, *J Urol*, 1991;146(1):36–9.
2. Pagano F, Bassi P, Galetti TP, et al., Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification, *J Urol*, 1991;145(1):45–50.
3. Wishnow KI, Levinson AK, Johnson DE, et al., Stage B (P2/3A/N0) transitional cell carcinoma of bladder highly curable by radical cystectomy, *Urology*, 1992;39(1):12–16.
4. Waehre H, Ous S, Klevmark B, et al., A bladder cancer multi-institutional experience with total cystectomy for muscle-invasive bladder cancer, *Cancer*, 1993;72(10):3044–51.
5. Vieweg J, Gschwend JE, Herr HW, Fair WR, The impact of primary stage on survival in patients with lymph node positive bladder cancer, *J Urol*, 1999;161(1):72–6.
6. Stein JP, Lieskovsky G, Cote R, Groshen S, et al., Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients, *J Urol*, 2001;19(3):666–75.
7. Dalbagni G, Genega E, Hashibe M, Zhang ZF, et al., Cystectomy for bladder cancer: a contemporary series, *J Urol*, 2001;165(4):1111–6.
8. Madersbacher S, Hochreiter W, Burkhard F, et al., Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy, *J Clin Oncol*, 2003;21(4):690–96.
9. Grossman HB, Natale RB, Tangen CM, et al., Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer, *N Engl J Med*, 2003;349(9):859–66.
10. Herr HW, Faulkner JR, Grossman HB, et al., Surgical factors influence bladder cancer outcomes: a cooperative group report, *J Clin Oncol*, 2004;22(14):2781–9.
11. Malmstrom PU, Rintala E, Wahlqvist R, et al., Five-year follow-up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial 1, *J Urol*, 1996;155(6):1903–6.
12. Sherif A, Rintala E, Mestad O, et al., Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer – Nordic Cystectomy Trial 2, *Scand J Urol*, 2002;36(6):419–25.
13. Bassi P, Pagano F, Pappagallo G, et al., Neo-adjuvant M-VAC of invasive bladder cancer: the GUONE multicenter phase III trial, *Eur Urol*, 1998;33(Suppl. 1):142.
14. Millikan R, Dinney C, Swanson D, et al., Integrated Therapy for locally advanced bladder cancer: Final Report of a Randomized Trial of Cystectomy Plus Adjuvant M-VAC Versus Cystectomy With Both Preoperative and Postoperative M-VAC, *JCO*, 2001;19(20):4005–13.
15. de Wit R, Overview of bladder cancer trials in the European Organization for Research and Treatment, *Cancer*, 2003;97(Suppl. 8):2120–26.
16. Hall RR, on behalf of the Intl Collaboration of Trialists of the MRC Advanced Bladder Cancer Group, Updated results of a randomised controlled trial of neoadjuvant cisplatin (C), methotrexate (M) and vinblastine (V) chemotherapy for muscle-invasive bladder cancer, *Proc Am Soc Clin Oncol*, 2002;21:abstract 710.
17. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists, *Lancet*, 1999;354(9178):533–40.
18. Griffiths G, Hall R, Sylvester R, International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial, *J Clin Oncol*, 2011;29(16):2171–7.
19. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration, *Eur Urol*, 2005;48(2):202–5.
20. Sonpavde G, Goldman BH, Speights VO, et al., Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy, *Cancer*, 2009;115(18):4104–9.
21. Wilkinson NW, Yothers G, Lopa S, et al., Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials, *Ann Surg Oncol*, 2010;17(4):959–66.
22. Canter D, Long C, Kutikov A, et al., Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy, *BJU Int*, 2011;107(1):58–62.
23. Dickstein RJ, Grossman HB, Pretzsch SM, et al., Can we reliably identify patients for radical cystectomy with neoadjuvant chemotherapy? Presented at the Annual Meeting of the Society of Urologic Oncology (9–10 December 2010, Bethesda, MD), abstr. 23.
24. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration, *Eur Urol*, 2005;48(2):189–99; discussion 99–201.
25. Stadler WM, Lerner SP, Groshen S, et al., Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status, *J Clin Oncol*, 2011;29(25):3443–9.
26. Souquet PJ, Krzakowski M, Ramlau R, et al., Phase I/II and pharmacokinetic study of intravenous vinflunine in combination with cisplatin for the treatment of chemonaive patients with advanced non-small-cell lung cancer, *Clin Lung Cancer*, 2010;11(2):105–13.
27. Davida KA, Milowsky MI, Ritchey J, Low Incidence of Perioperative Chemotherapy for Stage III Bladder Cancer 1998 to 2003: A Report From the National Cancer Data Base, *J Urol*, 2007;178(2):451–4.
28. Sternberg CN, de Mulder PH, Schornagel JH, et al., Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924, *J Clin Oncol*, 2001;19(10):2638–46.
29. von der Maase H, Hansen SW, Roberts JT, et al., Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study, *J Clin Oncol*, 2000;18(17):3068–77.
30. Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, et al., Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy, *J Clin Oncol*, 1999;17(10):3173–81.
31. Bellmunt J, Albanell J, Paz-Ares L, et al., Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine, *Cancer*, 2002;95(4):751–7.
32. Bajorin DF, McCaffrey JA, Dodd PM, et al., Ifosfamide, paclitaxel, and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules, *Cancer*, 2000;88(7):1671–8.
33. Bellmunt J, Guillem V, Paz-Ares L, et al., Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group, *J Clin Oncol*, 2000;18(18):3247–55.
34. Hussain M, Vaishampayan U, Du W, et al., Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer, *J Clin Oncol*, 2001;19(9):2527–33.
35. Bellmunt J, von der Maase H, Mead GM, et al., Randomized phase III study comparing paclitaxel-cisplatin-gemcitabine and gemcitabine-cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987, *J Clin Oncol*, 2012;30(10):1107–13.
36. Sternberg CN, de Mulder P, Schornagel JH, et al., Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours, *Eur J Cancer*, 2006;42(1):50–54.
37. Bamias A, Dafni U, Karadimou A, et al., Prospective, open-label, randomized, phase III study of two dose-dense regimens MVAC versus gemcitabine/cisplatin in patients with inoperable, metastatic or relapsed urothelial cancer: a Hellenic Cooperative Oncology Group study (HE 16/03), *Ann Oncol*, 2013;24(4):1011–17.
38. Loehrer P, Einhorn LH, Elson PJ, et al., A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a Cooperative Group Study, *J Clin Oncol*, 1992;10:1066–73.
39. Logothetis CJ, Dexeus FH, Finn L, et al., A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors, *J Clin Oncol*, 1990;8(6):1050–55.
40. Bamias A, Aravantinos G, Deliveliotis C, et al., Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group, *J Clin Oncol*, 2004;22(2):220–28.
41. Dreicer R, Manola J, Roth BJ, et al., Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium, *Cancer*, 2004;100(8):1639–45.
42. Bellmunt J, Theodore C, Demkov T, et al., Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract, *J Clin Oncol*, 2009;27(27):4454–61.
43. Bamias A, Karadimou A, Lampaki S, et al., Hellenic Cooperative Oncology Group, Athens, Greece. Prospective, randomised phase III study comparing two intensified regimens(methotrexate/vinblastin, doxorubicin hydrochloride/cisplatin(MVAC) versus gemcitabine/cisplatin) in patients with inoperable or recurrent urothelial cancer, *J Clin Oncol*, 2011;29(Suppl.;abstr 4510).
44. Galsky MD, Iasonos A, Mironov S, et al., Phase II trial of dose-dense doxorubicin plus gemcitabine followed by paclitaxel plus carboplatin in patients with advanced urothelial carcinoma and impaired renal function, *Cancer*, 2007;109(3):549–55.
45. Milowsky MI, Nanus DM, Maluf FC, et al., Final results of sequential doxorubicin plus gemcitabine and ifosfamide, paclitaxel, and cisplatin chemotherapy in patients with metastatic or locally advanced transitional cell carcinoma of the urothelium, *J Clin Oncol*, 2009;27(25):4062–7.
46. Gerlinger M, Swanton C, How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine, *Br J Cancer*, 2010;103(8):1139–43.
47. Culine S, Theodore C, De Santis M, et al., A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen, *Br J Cancer*, 2006;94(10):1395–401.
48. Vaughn DJ, Srinivas S, Stadler WM, et al., Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study, *Cancer*, 2009;115(18):4110–17.
49. Goldie JH, Coldman AJ, The genetic origin of drug resistance in neoplasms: implications for systemic therapy, *Cancer Res*, 1984;44(9):3643–53.
50. Azzoli CG, Temin S, Aliff T, et al., 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer, *J Clin Oncol*, 2011;29(28):3825–31.
51. NCCN, 2012. http://www.nccn.org/professionals/physician_gls/PDF/nsclc.pdf)
52. Behera M, Owonikoko TK, Chen Z, et al., Single agent maintenance therapy for advanced stage non-small cell lung cancer: A meta-analysis, *Lung Cancer*, 2012;77(2):331–8.