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# Treatment Decisions for Advanced Genitourinary Cancers: From Symptoms to Risk Assessment

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## Article info

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## Abstract

***Context:*** Current and emerging treatment options for advanced prostate, renal, and bladder cancer were discussed at the annual Interactive Genitourinary Cancer Conference (IGUCC) held in February 2009 in connection with the 2nd World Congress on Controversies in Urology (CURy).

***Objective:*** To provide practical clinical guidance for physicians and to promote the implementation of recent advances in the management of genitourinary cancers through closer collaboration among urologists, medical oncologists, and radiation oncologists.

***Evidence acquisition:*** This article was developed from presentations given at IGUCC 2009.

***Evidence synthesis:*** Docetaxel treatment is established as the standard first-line treatment for patients with metastatic castrate-resistant prostate cancer (mCRPC), based on improvements in overall survival regardless of age, performance status, and pain. Treatment should be introduced according to risk-factor assessment, clinical status, and patient values and preferences. Similarly, management of senior adults with mCRPC should be individually adapted to the patient's health status rather than chronologic age, especially since the benefits and toxicity associated with docetaxel treatment are similar in senior adults and younger patients. Asymptomatic patients with adverse prognostic factors for survival such as visceral metastases, anaemia, and new bone lesions may be candidates for chemotherapy. Prognostic nomograms based on pretreatment parameters aid in identifying patients for earlier chemotherapy. Second-line treatments for CRPC patients are needed, but currently no agent has demonstrated efficacy in phase 3 clinical trials. For patients with a prior response to docetaxel, retreatment at relapse can be effective and well tolerated.

There is a strong rationale for targeting angiogenesis in renal cell carcinoma (RCC), and new targeted therapies have changed treatment paradigms for RCC. In contrast, little progress has been made in the treatment of advanced bladder cancer since the introduction of cisplatin-based chemotherapy; new strategies are needed.

***Conclusions:*** Docetaxel (every 3 wk) treatment is a therapeutic option in elderly and asymptomatic mCRPC patients. Docetaxel retreatment is effective in initial responders.



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## 1. Introduction

The annual Interactive Genitourinary Cancer Conference (IGUCC), held in Lisbon, Portugal, in connection with the 2nd World Congress on Controversies in Urology (CURy), brought together urologists, medical oncologists, and radiation oncologists. The main goals of IGUCC 2009 were to provide attendees with the latest information on current and emerging treatment options for patients with advanced prostate cancer, renal cell carcinoma (RCC), and bladder cancer and to promote interactive exchanges among the multidisciplinary participants concerning their daily practice. Closer collaboration among urologists, medical oncologists, and radiation oncologists is critical to the successful implementation of recent clinical advances in the treatment of genitourinary cancers.

The meeting consisted of a combination of plenary sessions and interactive case studies presented by a faculty of experts from Europe and North America: John Fitzpatrick (chairman), Cora Sternberg, Fred Saad, Martine Extermann, Orazio Caffo, Susan Halabi, Gero Kramer, Stéphane Oudard, and Ronald de Wit.

## 2. Evidence acquisition

This article was developed from presentations given at IGUCC 2009.

## 3. Evidence synthesis

### 3.1. Prostate cancer

Prostate cancer is the most common form of cancer in Western men. In Europe, >345 000 new cases of prostate cancer were diagnosed in 2006, leading to 87 000 deaths [1], while an estimated 186 320 men in the United States were diagnosed with prostate cancer during 2008, leading to 28 660 deaths [2]. Prostate cancer inevitably becomes resistant to hormonal therapy, despite initially responding well in most cases. Castrate-resistant prostate cancer (CRPC) has a poor prognosis, with a median survival of 16–20 mo [3,4] and is frequently associated with painful bone metastases [5].

#### 3.1.1. Risk factors and treatment of patients with minimal pain

Prostate cancer has a heterogeneous biology, and survival depends on several prognostic factors, including ethnicity, performance status, Gleason score, presence of visceral metastases, pain at baseline, baseline prostate specific antigen (PSA), PSA doubling time (PSADT), haemoglobin, and alkaline phosphatase levels. The pivotal phase 3 TAX 327 study demonstrated improvements in overall survival for docetaxel (75 mg/m$^2$) plus prednisone administered every three weeks (D3P) compared with mitoxantrone plus prednisone (MP) in patients with metastatic CRPC (mCRPC) [3]. Additionally, improvements in quality of life, pain control, PSA decline, and objective tumour response were observed in men treated with D3P compared with MP.

These benefits were sustained at 3 yr [6], while benefits in overall survival were also confirmed in the phase 3 Southwest Oncology Group (SWOG) 9916 study, in which docetaxel was combined with estramustine [4]. Consequently, docetaxel-based chemotherapy is established as the standard first-line chemotherapy in men with mCRPC, and this has been highlighted in several guidelines (eg, European Association of Urology, European Society of Medical Oncologists, National Comprehensive Cancer Network, American Society of Clinical Oncology). Furthermore, docetaxel-treated patients reported consistent survival benefit in the TAX 327 study across diverse subgroup populations, regardless of the existence of substantial pain (defined by Present Pain Intensity score $\geq$2 and/or analgesic score $\geq$10) at baseline and performance status [6]. According to the updated survival analysis of the TAX 327 study, the hazard ratios for overall survival in patients with no or minimal pain and with substantial pain were 0.73 (95% confidence interval [CI]: 0.58–0.93, $p = 0.009$) and 0.85 (95% CI: 0.67–1.08, $p = 0.17$), respectively, for D3P compared with MP. Moreover, the median survival times for patients with no or minimal pain and with substantial pain were 23.0 mo ($p = 0.009$) and 14.9 mo ($p = 0.17$), respectively, for D3P compared with MP [6]. Asymptomatic patients may have adverse prognostic factors for survival such as visceral metastases, anaemia, new lesions on bone, and short PSADT that justify commencement of chemotherapy [7]. There is no reason to withhold treatment in asymptomatic patients who are prepared to receive active therapy.

Nomograms based on pretreatment parameters can facilitate identification of patients who may benefit from earlier treatment with chemotherapy. They also provide key insights into the disease process; facilitate design, conduct, and analysis of clinical trials; and are important tools for patient counselling. The strengths of nomograms include their easy implementation and more homogeneous grouping than risk grouping as well as greater predictive accuracy. Nomograms, however, can only be used when all of the relevant patient characteristics are available at baseline and when the assessed characteristics are within the lower and upper limits of the study population used to develop them. Furthermore, it is essential that chance is accounted for and 95% CIs reported, especially when informing patients and their families about risk.

Three prognostic nomograms (Cancer and Leukaemia Group B [CALGB] [8], Memorial Sloan-Kettering Cancer Centre [MSKCC] [9], and TAX 327 [10]) based on various prognostic factors (Table 1) have been developed for predicting median survival of patients with mCRPC. An online version of the CALGB nomogram has also been developed (URL: https://www.calgbapps.org/Nomogram/halabi.html). The CALGB and MSKCC nomograms predict survival probability at 1 and 2 yr, while the TAX 327 nomogram predicts survival probability at 1, 2, and 5 yr. The CALGB and MSKCC nomograms are based on pooled results from 6 and 19 smaller phase 2 clinical trials, respectively, involving men with mCRPC. In contrast, the TAX 327 nomogram is based solely on the large randomised phase 3 TAX 327 study and is the only nomogram based on a patient

**Table 1 – Comparison of prognostic factors included in metastatic castrate-resistant prostate cancer prognostic nomograms**

| Prognostic factors | CALGB | MSKCC | TAX 327 |
|---|---|---|---|
| PSA | X | X | X |
| Alkaline phosphatase | – | X | X |
| Haemoglobin | X | X | X |
| Performance status | ECOG | Karnofsky | Karnofsky |
| LDH | X | X | – |
| Gleason score | X | – | WHO |
| Presence of visceral disease | X | – | – |
| Age | – | – | X |
| Albumin | – | X | – |
| Treatment with docetaxel | – | – | X |
| Liver metastases | – | – | X |
| Pain at baseline | – | – | X |
| PSADT | – | – | X |
| Metastatic site | – | – | X |
| Type of progression | – | – | X |

CALGB = Cancer and Leukemia Group B; MSKCC = Memorial Sloan-Kettering Cancer Centre; PSA = prostate-specific antigen; ECOG = Eastern Cooperative Oncology Group; LDH = lactic dehydrogenase; WHO = World Health Organisation; PSADT = prostate-specific antigen doubling time.

population treated with docetaxel. Furthermore, only the TAX 327 nomogram examines the independent role of disease burden and PSA kinetics. The concordance indices of the CALGB, MSKCC, and TAX 327 nomograms are 0.68, 0.67, and 0.69, respectively, indicating imperfect discriminative abilities. The addition of biologic markers to future clinical studies may improve the predictive ability of prognostic nomograms.

**Discussion 1 – Interactive case study**

A patient with a 3-yr history of prostate cancer and currently receiving zoledronic acid presented with elevated PSA and three new bone metastases. Testosterone was at castrate levels, while alkaline phosphatase levels were twice the upper limit of normal. PSADT was <90 d, and there was no evidence of pain or visceral disease.

- Most delegates (51%) identified PSADT as the primary risk factor for assessing the patient's 1-yr survival probability. The faculty, however, noted that although pretreatment PSADT can predict overall survival, it cannot be used to predict the risk of death within 1 yr and requires considerable time to determine. Alkaline phosphatase levels (chosen by 2% of delegates) are important in the TAX 327 nomogram; they provide a good prognostic variable for disease extent and are particularly predictive of bone metastases. The presence of new bone metastases (9%), pain (17%), and visceral disease (12%) are also considered predictive of survival; however, the latter two variables were not present in the case history of this patient.
- Sixty percent of delegates chose to treat this patient by secondary hormonal manipulation; the remainder chose to initiate docetaxel treatment. The faculty noted that secondary hormonal manipulation has not been shown to affect overall survival, and there may be insufficient time for hormonal manipulation if a patient is rapidly progressing. Disease aggressiveness may be underestimated in patients with minimal pain.

*3.1.2. Senior adult population: Addressing the right treatment approach*

Management of prostate cancer in senior adults represents an important challenge. The mean age at diagnosis of prostate cancer is 71 yr in Europe and 68 yr in the United States [11,12]. Furthermore, the incidence of prostate cancer is steadily increasing, mainly due to greater numbers of men reaching advanced age [1]. Large numbers of patients could be denied treatment that may prolong survival and improve quality of life if misplaced concerns about tolerability resulted in a reluctance to initiate chemotherapy. This is especially relevant because increased life expectancy means that senior adults with prostate cancer are now at a real risk of dying from this disease.

The TAX 327 trial demonstrated a survival benefit in patients with mCRPC across all age groups [3,6]. The hazard ratios for overall survival in patients aged ≤68, ≥69, and ≥75 yr were 0.81 (95% CI: 0.64–1.02), 0.77 (95% CI: 0.61–0.98), and 0.80 (95% CI: 0.55–1.17), respectively, for D3P compared with MP. Furthermore, the toxicity associated with docetaxel treatment is similar in senior and younger patients with prostate cancer [13]. There was no difference in overall haematologic and nonhaematologic toxicity greater than grade 2 between patients aged ≥70 ($n$ = 52) and <70 ($n$ = 34) yr, according to analysis of pooled data from two phase 2 clinical trials of weekly docetaxel in men with mCRPC [13]. The tolerability of docetaxel administered every 3 wk, however, has not been specifically studied in vulnerable and frail senior adults, and weekly docetaxel in this setting also requires further evaluation.

There is large variation in the life expectancy, functional ability, health status, and ability to tolerate treatment in the senior population. Consequently, patient management should be individualised and not based solely on chronologic age. The International Society of Geriatric Oncology (SIOG) has recently proposed recommendations that address the current lack of specific guidelines for management of prostate cancer in senior adults (>70 yr old) [14]. The urologic approach to prostate cancer should be the same for both senior and younger patients, while treatment decisions should be based on an evaluation of patient health status (eg, comorbidities, nutrition, cognition, functional ability) and life expectancy. Fit or healthy senior patients should receive the same treatment as younger counterparts; vulnerable senior patients (ie, those with a reversible problem) should receive standard treatment after readaptation; frail senior patients (ie, those with an irreversible problem) should receive adapted treatment; patients who are "too sick" are candidates for symptomatic treatments.

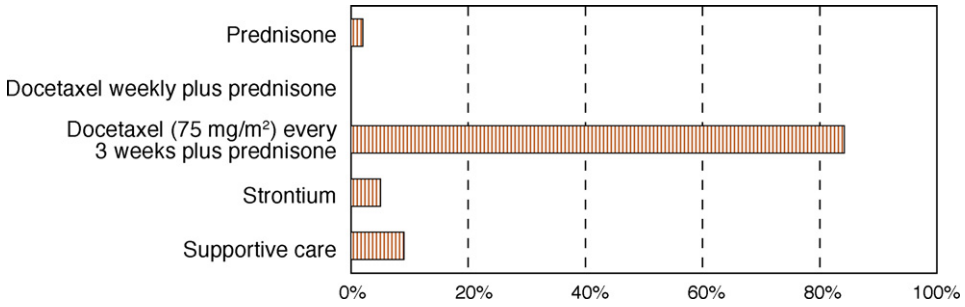


**Fig. 1 – Delegates' response to the question: What treatment approach would you proceed with?**

The prevalence and significance of comorbidities in senior adults has been highlighted in several studies [15–17]. Only 12% of patients aged ≥65 yr diagnosed with incident prostate cancer presented without comorbidity, disability, or geriatric syndromes in a recent cross-sectional study [17]; conversely, 24.7% of patients presented with all three issues. The most commonly reported comorbidities were cardiovascular disease, hypertension, and diabetes. Dementia, urinary incontinence, and depression represented the most common geriatric syndromes. Postoperative and late urinary complications after radical prostatectomy correlate significantly with the Romano-Charlson index, a weighted count of comorbidities [15]. Similarly, the addition of androgen suppression to radiation therapy did not prolong overall survival in patients with localised prostate cancer and moderate or severe comorbidities [16]. There was little impact on independence, comorbidity, and quality of life in elderly patients (≥70 yr of age) undergoing chemotherapy in a prospective pilot study [18]. Senior patients with prostate cancer should be stratified according to specific comorbidities in future randomised studies to determine the impact on survival and quality of life.

**Discussion 2 – Interactive case study**

An 82-yr-old man with CRPC who was previously active was now in pain and unable to enjoy an active life. His Mini-Mental State Examination (MMSE) score was 22 (lower limit of normal: 25).

- The MMSE is a valuable and quick cognitive screening tool for determining whether more in-depth testing is needed; low scores may result from depression, dementia, or delirium due to pain medication. Importantly, a low score may affect treatment compliance, and patients should be referred to a psychiatrist to determine the cause of a low score, although this referral should not delay treatment initiation. Proactive multidisciplinary supportive care to identify, monitor, and address the health status of senior adults is critical to successful management.
- The majority of delegates (84%) chose to treat this patient with docetaxel (75 mg/m$^2$) every 3 wk (Fig. 1). The remaining delegates chose to treat the patient with best supportive care (9%), strontium (5%), or prednisone (2%). The faculty noted that there is no evidence to support weekly docetaxel treatment on the basis of difference in toxicity compared to the every-3-wk regimen. Furthermore, weekly docetaxel (30 mg/m$^2$) did not significantly improve survival compared with mitoxantrone in the TAX 327 study.

*3.1.3. Retreatment of advanced prostate cancer: When and whom to consider?*

The establishment of standard second-line chemotherapy for men with mCRPC represents a significant unmet need, since earlier diagnosis and treatment means that many CRPC patients have a good performance status and desire additional treatment. But it is also important that first-line docetaxel treatment is not discontinued prematurely; in the TAX 327 study some docetaxel recipients experienced initial increases (≤12 wk) in serum PSA before subsequent decline [19]. Currently available drugs such as mitoxantrone and ixabepilone have only modest activity in the second-line setting [20]. Second-line satraplatin-based therapy did not significantly prolong overall survival in the phase 3 Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial, although statistically significant improvements in progression-free survival were reported [21]. Several additional phase 3 clinical studies are currently recruiting patients to examine other second-line treatment choices: the TROPIC trial (cabazitaxel, a new taxane, plus prednisone vs mitoxantrone plus prednisone), the SUN 1120 trial (sunitinib plus prednisone vs placebo plus prednisone) and the COU-AA-301 trial (abiraterone acetate plus prednisone/prednisolone vs placebo plus prednisone/prednisolone).

Retreatment with docetaxel after first-line relapse represents another option. The retrospective TRIADE study ($n$ = 148), based on seven phase 2 or 3 studies conducted in France in patients with mCRPC, supported the reintroduction of docetaxel at relapse in patients ($n$ = 50) who initially responded well to first-line docetaxel treatment [22]. The PSA response (decrease of ≥50%) in retreated patients was 48%, and the median overall survival was 16 mo; 14 patients (28%) were still alive at 2 yr. Docetaxel retreatment was also well tolerated, with nail disorders (12%) and oedema or weight gain (8%) the most commonly reported grade

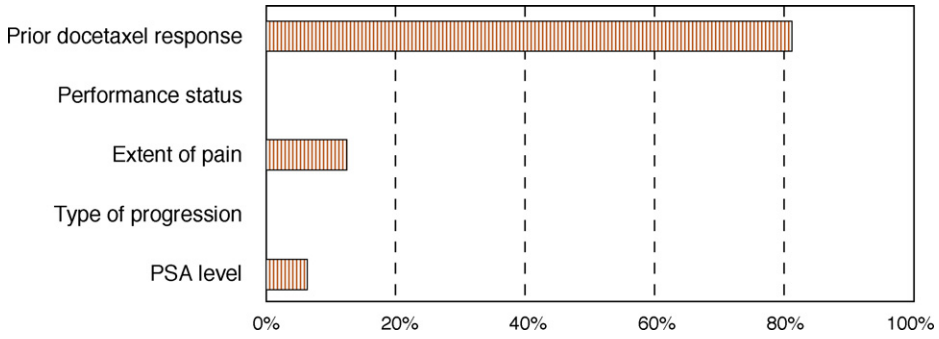


**Fig. 2 – Delegates' response to the question: What primary factor would you consider to assess the patient's severity of disease and future treatment?**

3–4 toxicities. Interestingly, results suggest that the addition of estramustine to docetaxel for second-line therapy may be effective in specific patient subpopulations that are resistant to docetaxel alone [23]. It is also notable that TAX 327 patients who crossed over to receive docetaxel after mitoxantrone reported better PSA response (decrease of ≥50%) and median progression-free survival (5.9 mo vs 3.4 mo) than vice versa [24].

Gero Kramer discussed the clinical experience of docetaxel retreatment at the Urology Department of the University of Vienna, Austria. A PSA response (decrease of >30%) was observed in approximately 50% of patients ($n = 31$) who were retreated with docetaxel for up to eight serial rounds, according to retrospective analysis. Initial treatment sequences consisted of six cycles in most cases. PSA response was greatest for patients who had a >20-wk holiday between retreatments, with 80% of patients exhibiting a >50% decrease in PSA compared with 37.5% of patients who had a holiday for <20 wk ($p = 0.017$). Consistent with these benefits, docetaxel induced significant increases in caspase-cleaved cytokeratin 18 (CK18) levels, a biomarker of tumour apoptosis, during second-, third- and fourth-line rounds of retreatment [25].

Orazio Caffo discussed the clinical experience of the Medical Oncology Department of the Santa Chiara Hospital, Trento, Italy. Patients ($n = 26$) who responded well to first-line docetaxel treatment without disease progression during chemotherapy were selected for further docetaxel treatment. Retreatment generally consisted of six or fewer cycles and was undertaken according to the same schedule as initial treatment. Patients who responded to second-line docetaxel treatment were usually retreated until real docetaxel resistance (ie, disease progression during docetaxel therapy) was observed. The PSA response rate (decrease of >50%) was 65% ($n = 17$), 40% ($n = 6$) and 25% ($n = 1$) after 1, 2, and 3 rounds of retreatment, respectively, while median survival from the first-line docetaxel treatment was 27 mo. The median treatment-free interval was 26 wk between the first and second rounds of retreatment and 19 wk between the second and third rounds of retreatment. Patient compliance was optimal, and no grade 3–4 toxicity was observed. Together, these results suggest that men who initially respond well to first-line docetaxel therapy can be effectively treated with docetaxel at relapse, although the number of retreatments and meaningful measurements of objective clinical benefits in the second-line treatment of CRPC still need to be established.

**Discussion 3 – Interactive case study**

A 65-yr-old male patient with mCRPC presented with pain, increased PSA, and four new bone metastases 6 mo after effective first-line docetaxel treatment.

- The majority of delegates (81%) identified previous docetaxel response as the primary factor for assessing the patient's disease severity and future treatment (Fig. 2). The remaining delegates chose the extent of pain (13%) or PSA level (6%).
- There was 100% consensus among delegates that the patient should be retreated with docetaxel. The faculty noted that the efficacy of docetaxel has been demonstrated using 10 cycles in the TAX 327 study and that there is no evidence that fewer cycles will produce the same overall survival benefit.

### *3.2. Renal cell carcinoma: What is on the horizon and beyond?*

Approximately 40 000 and 50 000 new cases of RCC are diagnosed in Europe and in the United States, respectively, each year [2,26]. Many patients with clinically localised disease relapse with advanced disease after surgery, while a significant proportion present with metastatic disease at initial diagnosis [27]. Metastatic RCC (mRCC) is highly resistant to standard chemotherapy, radiotherapy, and hormonal therapy, and, until recently, first-line treatment of mRCC was restricted to the cytokines, interferon (IFN) α and interleukin 2 (IL-2). Both of these agents are associated with low response rates (5–20%), a median overall survival of approximately 12 mo, and significant toxicity [28–32].

There is a clear rationale for targeted therapies in the setting of advanced RCC, since vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinases play a critical role in clear-cell carcinoma (the most common form of RCC) angiogenesis via involvement of the von Hippel-Lindau (VHL) tumour suppressor gene [33].

Consistent with this, targeted agents have demonstrated substantial benefits in first-line and second-line

**Table 2 – Current treatment options for advanced renal cell carcinoma**

| Agent | Setting | Progression-free survival |
|---|---|---|
| Sunitinib (VEGF and PDGF receptor tyrosine kinase inhibitor) | Untreated | 11 mo compared with 5 mo for IFN α [38] |
| Sorafenib (VEGF and PDGF receptor tyrosine kinase inhibitor) | Refractory to cytokine-based therapy | 5.5 mo compared with 2.8 mo for placebo in cytokine-refractory patients [34] |
| Bevacizumab (Monoclonal antibody to VEGF) | Untreated | 10.2 mo in combination with IFN α months compared with 5.4 mo for IFN α alone [35] |
| Temsirolimus (mTOR inhibitor) | Untreated (poor prognosis) | 3.8 mo compared with 1.9 mo for IFN α [36]; median overall survival was 10.9 mo compared with 7.3 mo for IFN α |
| Everolimus (mTOR inhibitor) | Refractory to sunitinib, sorafenib, or both | 4.0 mo compared with 1.9 mo for placebo [37] |

VEGF = vascular endothelial growth factor; PDGF = platelet-derived growth factor; IFN = interferon; mTOR = mammalian target of rapamycin.

**Table 3 – Treatment algorithm in 2009 for metastatic renal cell carcinoma**

| Setting | Patients | Therapy (level 1) | Other options (level 2 or higher) |
|---|---|---|---|
| Untreated | Good or intermediate risk | Sunitinib<br>Bevacizumab and IFN α | High-dose IL-2<br>Sorefanib<br>Clinical trial<br>Observation |
| | Poor risk | Temsirolimus | Sunitinib<br>Clinical trial |
| Refractory | Cytokine | Sorafenib | Sunitinib<br>Bevacizumab and IFN α |
| | VEGF–TKI<br>mTOR | Everolimus<br>Clinical trial | Clinical trial |

IFN = interferon; IL-2 = interleukin 2; VEGF = vascular endothelial growth factor; TKI = tyrosine kinase inhibitor; mTOR = mammalian target of rapamycin.

treatment of advanced RCC (Table 2) [34–38]. Targeted therapies are also better tolerated than cytokines. Consequently, systemic treatment of advanced RCC has undergone significant changes in the past few years (Table 3). Ongoing clinical trials are examining sequences of targeted therapies as well as horizontal and vertical targeted combination therapies designed to avert or overcome tumour resistance. Horizontal blockade inhibits multiple downstream pathways, while vertical blockade inhibits multiple sequential targets along a single pathway. Newer antiangiogenesis therapies such as axitinib and pazopanib are also being investigated in phase 3 clinical trials.

**Discussion 4 – Interactive case study**

A male patient with a 10-cm left renal mass had relapsed after radical nephrectomy and further surgery 1 yr later (this case occurred in 2005).

- The majority of delegates (87%) would have chosen to enrol him in a clinical study with a targeted therapy. The remaining delegates would have proceeded with high-dose IFN α (10%), IFN α and IL-2 (2%), or best supportive care (1%).

He was enrolled to a clinical trial and randomised to receive IFN α and relapsed after 8 mo of treatment.

- At this point, 98% of delegates chose to treat the patient with a targeted agent (extended-access programme with sunitinib). The remainder chose best supportive care.

### *3.3. Advanced bladder cancer: Past, present, and future chemotherapy regimens*

Bladder cancer is a common malignancy with an estimated 82 000 new cases diagnosed each year in Europe [1]. Cisplatin-based combination chemotherapy represents the historic standard treatment for patients with metastatic or unresectable bladder cancer. Two phase 3 studies have demonstrated the benefits of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) treatment, with an overall survival of 12–13 mo and good response rates of >40% [39,40]. Only 3.7% of M-VAC recipients, however, were disease free after 6 yr in a follow-up study [41], and this regimen is associated with significant toxicity and a treatment-related death rate of 3–4% [39,42]. Intensification of M-VAC dosage appears to be of little proven benefit to patients [43–45]. More recently, gemcitabine and cisplatin (GC) chemotherapy has emerged as an alternative to M-VAC: it provides similar benefits in long-term overall survival, time to disease progression, and response rates, with a more favourable toxicity profile [46,47]. The addition of paclitaxel to GC chemotherapy (PGC) did not significantly improve overall median survival (15.7 mo for PCG vs 12.8 mo for GC; $p = 0.10$) or median progression-free survival (8.4 mo for PCG vs 7.7 mo for GC; $p = 0.10$) in the European Organisation for Research and Treatment of Cancer (EORTC) 30987/Intergroup phase 3 study [48].

While novel three-drug regimens appear promising in phase 2 trials [49–51], randomised phase 3 trials are essential to demonstrate the efficacy of these regimens, since pretreatment prognostic factors can influence survival and response more than the treatment itself [52]. Indeed,

the survival times for advanced bladder cancer patients ($n = 203$) treated with M-VAC varied from 9.3 mo to 33 mo ($p = 0.0001$), depending on the presence of pretreatment risk factors (ie, Karnofsky performance status <80% and visceral metastasis) according to retrospective analysis [52]. Nevertheless, the maximum benefit with conventional cytotoxic agents may have been achieved, and new strategies are urgently needed.

The combination of gemcitabine and paclitaxel in M-VAC–refractory patients was well tolerated and effective, with a complete response of 28% [53]. This regimen was considerably more effective in patients who had received prior chemotherapy in the neoadjuvant or adjuvant setting compared with patients treated for metastatic disease, again highlighting the impact of patient selection. Vinflunine combined with best supportive care failed to demonstrate a consistent survival benefit compared with best supportive care alone in a recent phase 3 study [54]. A phase 3 trial (CILAB) comparing a new taxane, larotaxel, plus cisplatin and GC for first-line treatment of advanced bladder cancer is currently recruiting. Furthermore, several ongoing trials are currently investigating combination chemotherapy and targeted therapy, including an EORTC study that will evaluate GC chemotherapy with or without sorafenib.

**Discussion 5 – Interactive case study**

A male patient underwent a transurethral resection of the bladder (TURB) for a T1G3 tumour, followed by a second TURB for an in situ G3 tumour 6 mo later. An unconventional six doses of methotrexate, vinblastine, epirubicin, and cisplatin (M-VEC) were also administered.

- The majority of delegates (65%) chose to proceed with intravesical bacillus Calmette-Guérin (BCG) immunotherapy. The remaining delegates chose to repeat TURB (22%) or to perform a radical cystectomy (13%).

One year later, a third TURB was performed for a T2G3 tumour.

- At this point, 97% of delegates chose to perform a radical cystectomy. The remainder chose to repeat TURB (2%) or to perform a partial cystectomy (1%).

Almost 2 yr later, the patient developed a left pelvic mass.

- At this point, 53% of delegates chose to proceed with GC chemotherapy, 18% with gemcitabine and paclitaxel chemotherapy, 19% with radiotherapy, and 10% with M-VAC.

The patient exhibited a partial response after receiving gemcitabine/paclitaxel therapy.

- The majority of delegates chose to proceed with consolidative radiotherapy (64%). The remainder chose to enrol the patient in a clinical trial (16%) or to proceed with GC chemotherapy (20%).

## 4. Conclusions

Recent advances in the management of advanced prostate cancer, RCC, and bladder cancer using chemotherapeutic strategies were discussed at IGUCC 2009, while a number of challenging clinical cases demonstrated the importance of a multidisciplinary approach to urologic cancer.

The following conclusions were reached:

- Docetaxel administered at 75 mg/m$^2$ every 3 wk provides significant benefits in mCRPC patients, regardless of age and pain.
- Treatment decisions for senior adults should be based on patient health status rather than on chronologic age.
- Asymptomatic mCRPC patients with adverse prognostic factors are candidates for chemotherapy.
- Retreatment with docetaxel at relapse may be a therapeutic option for mCRPC patients who responded well to first-line docetaxel treatment.
- Targeted agents have demonstrated increases in overall survival and progression-free survival in first- and second-line treatment, respectively, of RCC.
- Clinical trials investigating targeted therapies in bladder cancer are finally under way.

## Conflicts of interest

John M. Fitzpatrick received consultancies and honoraria from sanofi aventis, Pfizer, GSK, Ipsen, Orion and Astra Zeneca. Fred Saad is an advisory board member, speaker, and researcher with sanofi aventis and Novartis. Martine Extermann received honoraria from sanofi aventis, Roche, and Amgen. Susan Halabi is a consultant with sanofi aventis. Gero Kramer has given honorary paid lectures and participated in the European Taxotere prostate cancer expert board meeting and the TOPAS trial (intermittent treatment with taxotere and prednisone in patients with asymptomatic hormone refractory prostate cancer, a multicentre phase 2 trial). Ronald de Wit received honoraria from sanofi aventis for consulting activities. The other authors have nothing to disclose.

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