Cancer Treatment Reviews 41 (2015) 699–706

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Beyond conventional chemotherapy: Emerging molecular targeted and immunotherapy strategies in urothelial carcinoma

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ARTICLE INFO

Article history:
Received 14 May 2015
Accepted 17 June 2015

Keywords:
Urothelial carcinoma
Targeted therapy
Immune therapy
Genetic aberrations

ABSTRACT

Advanced urothelial carcinoma is frequently lethal, and improvements in cytotoxic chemotherapy have plateaued. Recent technological advances allows for a comprehensive analysis of genomic alterations in a timely manner. The Cancer Genome Atlas (TCGA) study revealed that there are numerous genomic aberrations in muscle-invasive urothelial carcinoma, such as *TP53*, *ARID1A*, *PIK3CA*, *ERCC2*, *FGFR3*, and *HER2*. Molecular targeted therapies against similar genetic alterations are currently available for other malignancies, but their efficacy in urothelial carcinoma has not been established. This review describes the genomic landscape of malignant urothelial carcinomas, with an emphasis on the potential to prosecute these tumours by deploying novel targeted agents and immunotherapy in appropriately selected patient populations.

Introduction

Urothelial carcinoma (transitional cell carcinoma) is estimated to cause 150,000 deaths (world-wide) per year [1]. This type of cancer affects the urinary system, including the renal pelvis, ureters, bladder, urethra, and urachus [2]. It is the most common type of bladder cancer [2]. Approximately 75–80% of cases of urothelial tumours present with non-muscle invasive disease; however, the remaining cases of advanced (muscle-invasive) disease can show progression to metastatic disease that is often fatal. Environmental carcinogens, such as tobacco, aromatic amines, phenacetin, and arsenic, as well as chronic infection with *Schistosoma hematobium*, and male gender, are known risk factors [3,4]. Despite advances in treatment over past decades, therapy for metastatic disease is still limited and often fails. Therefore, it is important to consider alternative therapeutics in urothelial malignancy.

Currently, the most commonly used approach for the management of muscle-invasive urothelial carcinoma is multimodal therapy that combines surgery, radiation, and chemotherapy (Table 1) [5–12]. In muscle-invasive disease, neoadjuvant chemotherapy with standard-dose M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) is the standard of care based on results from prospective randomised phase III trials [5,6,13]. In the U.S. intergroup trial (Table 1), the standard-dose M-VAC followed by radical cystectomy for patients with muscle-invasive resulted in an increase of 31 months in median overall survival (OS) compared to the group without neoadjuvant chemotherapy (median OS: 77 months vs 46 months, $P = 0.06$ by a two-sided stratified log-rank test) [5]. Another randomised phase III controlled trial showed that neoadjuvant CMV (cisplatin, methotrexate, vinblastine) plus local therapy (either radical cystectomy or radiation) yielded a 6% absolute 10-year OS benefit compared to local therapy alone (10-year OS, 36% vs 30%; HR 0.84; 95% confidence interval [CI], 0.72–0.99). Meta-analysis of platinum-based combination neoadjuvant chemotherapy therapy showed about 5% absolute OS benefit at five years [14–16]. These studies established cisplatin-based combination neoadjuvant therapy as the standard of care in patients with muscle-invasive urothelial cancer. Chemoradiation demonstrated survival benefit in patients who are not candidate for surgery [17].

Multiple regimens have also been developed to improve survival in patients with metastatic urothelial cancer. Phase I and phase II trials with standard-dose M-VAC showed an overall response rate (RR) of approximately 70%, including clinical complete response (CR) in 36% of patients [18,19]. Subsequently, a phase III trial was conducted to compare standard-dose M-VAC and cisplatin alone or CISCA (cisplatin, cyclophosphamide, and adriamycin). M-VAC was superior to either cisplatin alone or CISCA, and showed an absolute OS benefit of 3–4 months. [7,8] In studies of a dose-dense regimen with growth factor support,

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http://dx.doi.org/10.1016/j.ctrv.2015.06.004
0305-7372/

Table 1
Standard therapy for advanced urothelial carcinoma [5–12].

Stage	Therapy	Outcome	*P* value
Muscle-invasive disease	Standard dose-MVAC + radical cystectomy vs radical cystectomy only [5]	Median OS: 77 mo vs 46 mo	*P* = 0.06 (two-sided)
	Cisplatin, methotrexate, and vinblastine + local therapy vs local therapy only [6]	10 year OS: 36% vs 30%	HR 0.84 (95% CI, 0.72–0.99)
Metastatic disease	Standard dose-MVAC vs cisplatin [7]	Median OS: 12.5 mo vs 8.2 mo	*P* = 0.002
	Standard dose-MVAC vs CISCA [8]	Median OS: 12 mo vs 9 mo	N/A
	Standard dose-MVAC vs dose dense-MVAC [9,10]	5 year OS: 14% vs 22%	*P* = 0.042
	Standard dose-MVAC vs gemcitabine plus cisplatin [11]	Median OS: 14.8 mo vs 13.8 mo	*P* = 0.75
	Gemcitabine plus cisplatin vs paclitaxel, gemcitabine, and cisplatin [12]	Median OS: 12.7 mo vs 15.8 mo	*P* = 0.75

Abbreviations: CISCA = cisplatin, cyclophosphamide, and adriamycin; CMV = cisplatin, methotrexate, and vinblastine; HR = hazard ratio; mo = months; M-VAC = methotrexate, vinblastine, adriamycin, and cisplatin; N/A = not available; OS = overall survival; vs = versus.

dose-dense M-VAC showed a superior CR rate (25% vs 11%, *P* = 0.009) and a superior RR (72% vs 58%, *P* = 0.016) compared to standard-dose M-VAC [9,10]. Median OS was slightly improved in the dose-dense regimen (15.1 months vs 14.9 months; HR 0.76, 95% CI: 0.58–0.99), and the 5-year survival rate was superior in the dose-dense arm (26.2% vs 13.5%; 95% CI, 0.15–0.29). Grade 3 and grade 4 toxicities were less common in the dose-dense regimen, especially in neutrophil counts. In another study, the combination of gemcitabine and cisplatin was compared to standard-dose M-VAC in a phase III setting with similar median progression free survival (PFS) (7.4 months vs 7.4 months) and median OS (13.8 months vs 14.8 months, *P* = 0.75), but with fewer toxicities [20]. Addition of paclitaxel to the combination of gemcitabine and cisplatin resulted in a higher RR (55.5% vs 43.6%, *P* = 0.0031), and higher toxicity but no OS benefit (median OS, 15.8 months vs 12.7 months, *P* = 0.75) [12]. These studies established the combination of gemcitabine and cisplatin or M-VAC as the standard of therapy in metastatic urothelial carcinoma.

Although these results confirm that the combination chemotherapy improves outcomes, the overall benefit is modest, and alternative therapies are needed to significantly improve the prognosis of patients with metastatic urothelial carcinoma. Deployment of immunotherapy or matched targeted therapy approaches based on molecular profiles has resulted in significant benefits to patients with a variety of cancers ranging from chronic myelogenous leukaemia to lung cancer [21,22]. We therefore reviewed the molecular landscape of urothelial carcinoma and its implications for molecularly targeted and immunotherapeutic approaches.

Genomic alterations in urothelial malignancy

The advances in technology over recent decades have made it possible to capture genomic alterations in cancer. In urothelial carcinoma, whole genome sequencing studies have revealed both well-characterised and novel genomic alterations, with extensive work performed in more advanced disease [23–26]. The most commonly altered genes in muscle-invasive urothelial carcinoma are listed in Table 2 and Fig. 1 [27–65].

TP53

The p53 protein, encoded by the *TP53* gene on chromosome 17p13.1, regulates DNA repair, apoptosis, senescence, growth arrest, and metabolic homeostasis [27]. P53 functions as a tumour suppressor through transcriptional activation of the p21 cyclin-dependent kinase inhibitor (CDKI) and subsequent inhibition of the G1-S cell cycle transition [66,67]. In the TCGA study data set, approximately 59% of patients had a genomic alteration in this gene (Table 2), making it the most commonly altered gene [25]. Heterozygosity at the 17p locus, with loss of function of the second allele, leads to a paradoxical stabilisation and overexpression of the defective protein in the nucleus of bladder cancer cells, leading to ready assessment of p53 status by immunohistochemistry in more than 90% of mutated cases [68,69]. Assessment of the *TP53* gene by sequencing or immunohistochemistry lends itself to a unique targeted therapy approach using Wee-1 inhibitors such as MK-1775 [28,29], although its efficacy has not yet been studied in urothelial carcinoma. Wee1 is a tyrosine kinase that phosphorylates and inactivates CDC2 and is involved in G2 checkpoint signalling. Because p53 is a key regulator in the G1 checkpoint, p53-deficient tumours rely only on the G2 checkpoint after DNA damage. Hence, such tumours are selectively sensitised to DNA-damaging agents by Wee1 inhibition. In addition, recent retrospective data suggest that patients with *TP53* mutations may benefit from anti-angiogenesis agents such as bevacizumab, perhaps because TP53 inhibits the transcription of VEGF-A (the target of bevacizumab), which may be upregulated in the presence of the mutation [30,70]. Bevacizumab demonstrated a RR in renal cell carcinoma of approximately 31% [71].

MLL2

The *MLL2* gene (also called *KMT2D*) is a histone methyltransferase and a key regulator of histone H3 lysine 4 residue methylation [31]. Mutations in *MLL2* are present in approximately 27% of urothelial carcinoma cases [25]. Menin-MLL inhibitor is a promising agent to target *MLL2* aberrations and has demonstrated activity in a pre-clinical acute leukaemia model [32].

ARID1A

The *ARID1A* gene is a DNA-binding subunit of SWI/SNF complexes and regulates gene expression through chromatin remodelling [33]. About 25% of urothelial carcinoma showed loss-of-function mutations of *ARID1A* [25]. Currently, no agent specifically targets the chromatin remodelling function of *ARID1A*. Recent data, however, suggest that *ARID1A* mutation can also sensitise cells to PI3K and AKT inhibitors, providing a venue for actionability [34].

KDM6A

The *KDM6A* gene (also known as *UTX*) is a histone demethylase specific for histone H3 Lysin 27 and regulates gene transcription [35]. In approximately 24% of urothelial carcinoma, *KDM6A* is altered. There is no available targeted agent for *KDM6A*.