ELSEVIER

Critical Reviews in Oncology/Hematology 96 (2015) 81–90

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Emerging concepts on drug resistance in bladder cancer: Implications for future strategies

Francesco Massari [a], Matteo Santoni [b,*], Chiara Ciccarese [a], Matteo Brunelli [c], Alessandro Conti [d], Daniele Santini [e], Rodolfo Montironi [f], Stefano Cascinu [b], Giampaolo Tortora [a]

[a] *Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Verona, Italy*
[b] *Medical Oncology, AOU Ospedali Riuniti, Polytechnic University of the Marche Region, Ancona, Italy*
[c] *Department of Pathology and Diagnostic, A.O.U.I., University of Verona, Verona, Italy*
[d] *Department of Clinic and Specialistic Sciences—Urology, Polytechnic University of the Marche Region, Ancona, Italy*
[e] *Department of Medical Oncology, Campus Bio-Medico University of Rome, Rome, Italy*
[f] *Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, AOU Ospedali Riuniti, Ancona, Italy*

Accepted 5 May 2015

Contents

1. Introduction . . . 82
2. Resistance to cisplatin . . . 82
   2.1. ERCC1 . . . 82
   2.2. Poly(ADP-ribose) polymerase (PARP) . . . 83
   2.3. Nuclear factor erythroid 2–related factor2 . . . 83
   2.4. Copper transporter 1 (CTR1) . . . 84
   2.5. MicroRNAs (miRNAs) . . . 84
   2.6. Epithelial-mesenchymal transition (EMT) . . . 84
   2.7. p53 . . . 84
3. Resistance to gemcitabine . . . 84
4. Resistance to taxanes . . . 85
5. Resistance to vinflunine . . . 86
6. Resistance to targeted agents . . . 86
   6.1. Resistance to epidermal growth factor receptor (EGFR) inhibitors . . . 86
   6.2. Resistance to fibroblast growth factor receptor (FGFR) . . . 87
   6.3. Resistance to VEGF/VEGFR inhibitors . . . 87
7. Conclusion . . . 87
   Table of contents . . . 88
   Founding source statement . . . 88
   Conflict of interest statement . . . 88
   Financial disclosures . . . 88
   References . . . 88
   Biography . . . 90

Summary

The combination chemotherapies with methotrexate plus vinblastine, doxorubicin and cisplatin (MVAC or CMV regimens) or gemcitabine plus cisplatin represent the standard as first-line therapy for patients with metastatic urothelial cancer. In Europe, vinflunine is an option for

* Corresponding author. Tel.: +39 0715964263; fax: +39 0715964269.
E-mail address: mattymo@alice.it (M. Santoni).

http://dx.doi.org/10.1016/j.critrevonc.2015.05.005
1040-8428/© 2015 Elsevier Ireland Ltd. All rights reserved.

second-line therapy for patients progressed during first-line or perioperative platinum-containing regimen. Alternative regimens containing taxanes and/or gemcitabine may be valuated case by case. Furthermore, carboplatin should be considered in patients unfit for cisplatin both in the first and second-line setting. Based on these findings, a better comprehension of the mechanisms underlying the development of drug resistance in patients with bladder cancer will represent a major step forward in optimizing patients' outcome. This article reviews the current knowledge of the mechanisms and emerging strategies to overcome resistance in patients with advanced urothelial cancer.
© 2015 Elsevier Ireland Ltd. All rights reserved.

Keywords: Drug resistance; Bladder cancer; Personalized medicine

1. Introduction

Bladder cancer is the fourth most frequent cancer in men in developed countries [1]. It is more prevalent in men than women, with a median age at diagnosis of 65 years [2]. Bladder cancer is clinically divided into muscle-invasive (MI-BC) and nonmuscle-invasive (NMI-BC), based on invasion of the lamina propria. NMI-BC is often multifocal, accounts for 80% of urothelial carcinomas, whereas MI-BC accounts for about 20% and is characterized by high occurrence rate of distant metastases, even after radical cystectomy and systemic chemotherapy.

The combination chemotherapies with methotrexate plus vinblastine, doxorubicin and cisplatin (MVAC or CMV regimens) or gemcitabine plus cisplatin represent the standard as first-line therapy for patients with metastatic urothelial cancer [3]. The median overall survival (OS) of patients with advanced disease is approximately 14 months [4], while median progression free survival (PFS) of cisplatin-based first-line therapy ranges from 7 to 9 months [4].

Although bladder cancer is a relatively chemosensitive tumor, showing a response rate of 50–70% to frontline treatments, patients who recur after first-line chemotherapy have a very poor prognosis [5]. Interestingly, a tumor response to prior chemotherapy seems to not affect the outcome of patients treated with second-line chemotherapy, with a PFS that does not overcome 3 months for both patients with or without response to chemotherapy [6]. In addition, after failure of cisplatin-based first-line therapy, there is no consensus in the management of cisplatin-resistant bladder cancer. In Europe, vinflunine is a second-line option for patients progressed during first-line or perioperative platinum-containing regimen [7]. Alternative regimens containing taxans and/or gemcitabine can be valuated case by case [8,9]. The median PFS of second-line treatments ranges from approximately 3 to 4 months [8,9,6]. Furthermore, carboplatin should be considered in patients unfit for cisplatin both in the first and second-line setting, although it results less effective in these patients [10].

Based on these findings, a better comprehension of the mechanisms underlying the development of drug resistance in patients with bladder cancer will represent a major step forward in optimizing patients' outcome. This article reviews the current knowledge of the mechanisms and emerging strategies to overcome resistance in patients with advanced urothelial cancer.

2. Resistance to cisplatin

Resistance to cisplatin-based chemotherapy is a major obstacle to bladder cancer treatment. Its cytotoxic effects are mainly due to the formation of DNA inter- and intra-strand adducts, which interfere with DNA replication and transcription. Increased drug efflux, reduced influx, increased DNA repair and tolerance to DNA lesions seem to be the predominant mechanisms of cisplatin resistance. A description of these mechanisms is mentioned below (Fig. 1).

2.1. ERCC1

The nucleotide excision repair (NER) system is a cellular DNA damage response induced to remove cisplatin-DNA adducts, and therefore is considered one of the determinants of cisplatin resistance [11]. Excision repair cross complementing group 1 (ERCC1) is a member of the NER family. This enzyme is a single strand-specific endonuclease required to repair the DNA lesions induced by UV light or due to electrophilic compounds including cisplatin. ERCC1 forms a heterodimer with the xeroderma pigmentosum complementation group F (XPF) endonuclease (also known as ERCC4), and this complex catalyzes the 5′ incision in the process of excising the DNA lesion [12].

ERCC1 protein expression has been associated with *in vitro* resistance to cisplatin-based chemotherapy by Usanova et al. They observed an increased sensitivity to cisplatin in MGH-U1 bladder cancer cell line after the down-regulation of ERCC1-XPF [13]. In the same view, Bellmunt et al. showed that ERCC1 expression was correlated with the outcome of patients treated with platinum-based regimen [14]. Indeed, median OS was longer in patients with low expression of ERCC1 mRNA compared to higher levels (25.47 vs. 15.40 months).

Immunohistochemistry with monoclonal antibody 8F1 is the standard method to evaluate ERCC1 protein expression, although novel antibodies have been recently evaluated [15]. Presently, it is still debated if a scoring system based on the relative expression of ERCC1, without accounting for the proportion of tumor cells with each expression level (*e.g.* by H-score), may be appropriate to evaluate a predictive effect of ERCC1 expression on the response to cisplatin-based regimens. Indeed, even the presence of a small proportion of tumor cells with high ERCC1 expression

Download English Version:

https://daneshyari.com/en/article/3328639

Download Persian Version:

https://daneshyari.com/article/3328639

Daneshyari.com