Cancer Treatment Reviews 39 (2013) 388–401

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

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

Complications of Treatment

A contemporary update on rates and management of toxicities of targeted therapies for metastatic renal cell carcinoma

Ahmed Alasker [a,d,1], Malek Meskawi [a,*,1], Maxine Sun [a], Salima Ismail [a,d], Nawar Hanna [a,d], Jens Hansen [a,c], Zhe Tian [a], Marco Bianchi [a,b], Paul Perrotte [d], Pierre I. Karakiewicz [a,d]

[a] Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada
[b] Department of Urology, Urological Research Institute, Vita-Salute San Raffaele University, Milan, Italy
[c] Martini-Clinic, Prostate Cancer Center Eppendorf-Hamburg, Hamburg, Germany
[d] Department of Urology, University of Montreal, Montreal, Canada

ARTICLE INFO

Article history:
Received 28 June 2012
Received in revised form 3 December 2012
Accepted 7 December 2012

Keywords:
Side effects
Targeted therapy
Renal cell carcinoma
Adverse events

ABSTRACT

Background: To provide an updated review of adverse events associated with sunitinib, pazopanib, bevacizumab, temsirolimus, axitinib, everolimus and sorafenib and their management.
Materials and methods: We performed a PubMed and Cochrane-based review of side effects associated with the seven agents including product monographs to provide an outline of treatment measures aiming to reduce their toxicities. Subject and outcome of interest, design type, sample size, pertinence and quality, and detail of reporting were the indicators of manuscript quality.
Results: All targeted therapies cause adverse events. Most adverse events may be prevented or tested before they escalate to severe levels.
Conclusion: Prevention, early recognition, and prompt management of side effects are of key importance and avoid unnecessary dose reductions, which may undermine treatment efficacy.

Introduction

A paradigm shift occurred in the management of metastatic renal cell carcinoma (mRCC) with the advent of novel biological agents targeting vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways. The advent of these agents prompted a considerable improvement in progression-free survival (PFS) and overall survival (OS) of mRCC patients in recent years. This was contingent upon the use, efficacy and tolerability of several sequential targeted therapies (TTs).[1–13] Of those, four agents (sunitinib, bevacizumab, temsirolimus and pazopanib) demonstrated efficacy in first-line therapy.[1–8] Three other agents (sorafenib, axitinib and everolimus) showed efficacy in second or subsequent treatment lines.[9–13]

However, toxicity and suboptimal tolerability of some agents may undermine their benefits. In consequence, early identification, prevention and/or treatment of toxicities are crucial to maximize their efficacy. Based on these considerations, we provide an exhaustive and comprehensive assessment of toxicities that may be expected with each of these agents. Additionally, we provide an outline of toxicity management to ensure tolerability and the attainment of maximal efficacy.

Materials and methods

We performed a systematic English language literature review using the keywords "bevacizumab," "sorafenib," "sunitinib," "temsirolimus," "everolimus," "pazopanib," "axitinib", "toxicity," "adverse effects," and "side effects" within the PubMed and Cochrane. The search was limited to English literature, humans, and persons aged 18 years and older. Subject and outcome of interest, design type, sample size, pertinence and quality, and detail of reporting were the indicators of manuscript quality. Due to availability of only one phase III trial for each of addressed molecules, except for bevacizumab and sorafenib with more than one phase III trial available, all phase III data were included in the current manuscript.[1–13] Moreover, individual patient data were not considered. As a result, strict adherence to the Oxman criteria,[14] which is based on a Overview Quality Assessment Questionnaire (OQAQ) of

* Corresponding author. Address: Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center (CHUM), 264 Boul. Rene-Levesque East, Suite 228, Montreal QC, Canada H2X 1P1. Tel.: +1 514 890 8000x35336; fax: +1 514 227 5103.
E-mail addresses: ahmed.alasker@umontreal.ca (A. Alasker), malek.meskawi@gmail.com (M. Meskawi), maxine.sun@gmail.com (M. Sun), ismail.salima@gmail.com (S. Ismail), nawarhanna10@gmail.com (N. Hanna), jenshansen81@gmail.com (J. Hansen), zhe.tian24@gmail.com (Z. Tian), bianchihsr@gmail.com (M. Bianchi), paul.perrotte@umontreal.ca (P. Perrotte), pierre.karakiewicz@umontreal.ca (P.I. Karakiewicz).
[1] These authors contributed equally to this work.

0305-7372/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2012.12.006

10 items relating to the methodological quality, could not be applied. Such items include the search methods, inclusion criteria, the avoidance of bias, the validity of the included studies, methods on combining results and drawing appropriate conclusions. The higher OQAQ score, the greater quality of the review. Recommendations were retrieved from various sources, such as the National Comprehensive Cancer Network Guidelines and National Heart, Lung and Blood Institute. The search was completed by three authors (A.A., M.S. and M.M.). For each specific toxicity or toxicity group, we outlined a structured approach for early symptoms recognition, prevention, and management. Toxic side effects were graded according to the Common Toxicity Criteria v.3.0 of the United States National Cancer Institute.[15]

Results

Toxicities of first line agents

Sunitinib is an orally administered inhibitor of tyrosine kinases including VEGF and platelet-derived growth factor (PDGF) receptors. Within a phase III trial ($n = 750$), sunitinib improved PFS from 5 to 11 months in first line for patients with mRCC.[1,2] The most common clinical toxicities recorded for sunitinib were diarrhea (61%), fatigue (54%), nausea (44%), anorexia (34%), vomiting (31%), hypertension (30%), stomatitis (30%), and hand–foot syndrome (29%). Of those, hypertension (12%), fatigue (11%), diarrhea (9%) and hand–foot syndrome (9%) represented grade 3–4 (G3–4) toxicities.[1,2] Most frequent laboratory toxicities consisted of leucopenia (78%), neutropenia (77%), and anemia (79%). Of those, neutropenia (18%), lymphopenia (18%), increased lipase (18%) and increased uric acid (14%) represented main G3–4 toxicities (Table 1).[1,2] Similar rates were recorded in the expanded access sunitinib trial ($n = 4564$).[16]

Pazopanib is a novel oral angiogenesis inhibitor targeting VEGF receptor, PDGF receptor, and c-Kit. The phase III trial ($n = 435$) showed a PFS of 9.2 vs. 4.2 months for pazopanib relative to placebo in either first line (54%) or cytokine pre-treated (46%) mRCC patients.[3] The most common clinical toxicities were diarrhea (52%), hypertension (40%), hair discoloration (38%), nausea (26%), and anorexia (22%). Of those, hypertension (4%), diarrhea (3%), and asthenia (3%) represented G3–4 toxicities.[3] Most frequent laboratory toxicities were alanine transferase (ALT) (53%; G3–4: 12%) and aspartate aminotransferase (AST) (53%; G3–4: 8%) increases, as well as hyperglycemia (41%; G3–4: <1%) (Table 1).[3]

Bevacizumab is an intravenously administered humanised monoclonal antibody that directly inhibits circulating VEGF. In the AVOREN phase III trial ($n = 649$), bevacizumab/interferon (bev/IFN) improved PFS from 5.4 to 10.2 months relative to IFN alone.[4,5] The PFS benefit was 8.5 vs. 5.2 months in the North American CALBG trial ($n = 732$).[6,7] Based on both trials, the most common clinical toxicities for bevacizumab/IFN were pyrexia (45%), anorexia (17–36%), fatigue (33–37%), bleeding (6–33%), and hypertension (26–28%). Of those, fatigue (12–37%), anorexia (3–17%), and hypertension (3–11%) represented G3–4 toxicities.[4–7] Most frequent laboratory toxicities were proteinuria (18–71%) and neutropenia (7–43%). Of those, proteinuria (7–15%) and neutropenia (4–9%) represented G3–4 toxicities (Table 1).[4–7] These rates may be due to the combination of bevacizumab and IFN. The latter is associated with a high toxicity profile according to phase II studies.[17]

Temsirolimus, an intravenously administered inhibitor of mTOR, improved overall survival from 1.9 to 3.8 months relative to interferon in mRCC patients.[8] The temsirolimus phase III trial ($n = 626$) focused on all histologic mRCC subtypes in poor-risk patients.[8] In consequence, patients were more prone to experience treatment-related toxicities. The most common clinical toxicities were fatigue (51%; G3–4: 11%), rash (47%; G3–4: 4%), nausea (37%; G3–4: 2%), and anorexia (32%; G3–4: 3%).[8] The main laboratory toxicities consisted of dyslipidemia (52%), anemia (45%), and hyperglycemia (26%). Of those, anemia (20%), hyperglycemia (11%), and neutropenia (3%) represented G3–4 toxicities (Table 1).[8]

Toxicities of second or subsequent line agents

Axitinib (AG-013736) is an oral, selective, second generation inhibitor of VEGF 1, 2 and 3. In the phase III trial (AXIS) ($n = 723$), axitinib improved PFS from 4.7 to 6.7 months relative to sorafenib, as second line treatment for mRCC patients following failure of previous systemic therapy (sunitinib (54%), cytokine (35%), bevacizumab (8%), temsirolimus (3%)).[9] The most common adverse events for axitinib were diarrhea (55%), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%), and dysphonia (31%). Of those, hypertension (16%), diarrhea (11%), and fatigue (11%) represented G3–4 toxicities.[9] The main laboratory abnormalities consisted of creatinine elevation (55%), hypocalcaemia (39%), anemia (35%) and lymphopenia (33%). Of those, lipase elevation (5%), lymphopenia (3%) and hypophosphatemia (2%) represented G3–4 toxicities (Table 1).[9]

Everolimus is an orally administered inhibitor of mTOR. It prolonged PFS from 1.9 to 4.9 months relative to placebo in second line (74%) or third line (26%) therapy.[10,11] The most common clinical toxicities were stomatitis (44%), rash (29%), fatigue (31%), diarrhea (30%), and anorexia (25%). Of those, stomatitis (4%), fatigue (5%), and pneumonitis (4%) represented G3–4 toxicities.[10,11] The most frequent laboratory toxicities consisted of dyslipidemia (77%), anemia (92%), and hyperglycemia (57%). Of those, lymphopenia (18%), hyperglycemia (12%), and anemia (13%) represented G3–4 toxicities (Table 1).[10,11] Similar rates were reported in the expanded access everolimus trial ($n = 1367$).[18]

Sorafenib is an orally active multikinase inhibitor. In the phase III trial ($n = 903$) conducted by the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), sorafenib improved PFS from 2.8 to 5.5 months relative placebo after cytokine failure.[12,13] In the AXIS trial ($n = 723$), sorafenib PFS was 4.7 vs. 6.7 months for axitinib, in second line treatment of mRCC.[9] The most common clinical toxicities of any grade for sorafenib were diarrhea (43–53%), rash (32–40%), fatigue (37%), hand–foot syndrome (HFS) (30–51%), and alopecia (27–32%). Of those, HFS (6–16%), fatigue (3–5%), dyspnea (4%), and hypertension (4–11%) represented G3–4 toxicities.[9,12,13] The most common laboratory toxicities were anemia (8–52%; G3–4: 4%), increased lipase (46%; G3–4: 15%) and lymphopenia (36%; G3–4: 4%) (Table 1). [9,12,13] Similar rates were recorded in the European ($n = 1159$)[19] and North American ($n = 2504$)[20] expanded access sorafenib trials.

Prevention and/or management of specific toxicity

Constitutional toxicities

Fatigue. Fatigue (Table 1) is often multifactorial in cancer patients. Thus, other potential causes such as anemia, sleep disturbances, nutritional deficits, electrolyte abnormalities (hypophosphatemia, hypomagnesemia, etc.), decreased functional status and comorbidities should be considered in patients with treatment-related fatigue.

Fatigue management may be non-pharmacological: activity enhancement, psychosocial interventions (cognitive behavioral therapy, psycho-educational therapy, supportive expressive therapy) or pharmacological (Table 2). Psychostimulants (methylphenidate, modafenil) or prednisone 5–10 mg may be