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Review

Examining the bleeding incidences associated with targeted therapies used in metastatic renal cell carcinoma

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ABSTRACT

A systematic review was conducted to illustrate the bleeding risks associated with targeted therapies used in the treatment of metastatic renal cell carcinoma (mRCC). Eligible studies included phase II, III, or IV clinical trials using pazopanib, sunitinib, cabozantinib, lenvatinib, everolimus, temsirolimus, bevacizumab, axitinib, and/or sorafenib in the setting of mRCC. Types of bleeding event(s), bleeding event frequency, and incidence of thrombocytopenia were collected from the relevant articles. ClinicalTrials.gov was also searched for incidence of "Serious bleeding adverse effects" reported in these trials. The incidences of bleeding events ranged from 1 to 36%, and incidences of thrombocytopenia ranged from 2 to 78%. Available serious bleeding adverse events ranged from 1 to 7%. The highest percentage of bleeding incidences were seen with bevacizumab, while the lowest percentage of bleeding incidences were seen with axitinib. All of the included trials were of high quality per Jadad scoring.

1. Background

Targeted therapies are the mainstay of treatment for metastatic renal cell carcinoma (mRCC) (National Comprehensive Cancer Network, 2017). These agents inhibit common molecular pathways that are dysfunctional in mRCC including the vascular endothelial growth factor (VEGF) and mechanistic target of rapamycin (mTOR) pathways. Food and Drug Administration (FDA)-approved therapies for mRCC that inhibit the VEGF pathway include pazopanib, sunitinib, cabozantinib, lenvatinib, bevacizumab, axitinib, and sorafenib (National Comprehensive Cancer Network, 2017). Therapies approved for mRCC that block the mTOR pathway include everolimus, and temsirolimus (National Comprehensive Cancer Network, 2017).

Medications that inhibit the VEGF pathway have multiple side effects secondary to the disruption of angiogenesis. Thrombotic complications with VEGF inhibitors have been studied and published in the literature (Sonpavde et al., 2013). However, bleeding events have not been reported as consistently. Further investigation is needed to help clinicians decide which therapy to choose when a patient is at an increased risk of hemorrhagic events. This systematic review was conducted to provide contemporary information on bleeding events observed with the use of targeted therapies for treatment of mRCC.

2. Methods

2.1. Selection

A search was conducted using PubMed/Medline from January 2001 through March 2016, to identify prospective clinical trials that reported rates of bleeding complications in patients with mRCC treated with agents approved by the FDA for this indication. Key terms used included: pazopanib, sunitinib, cabozantinib, lenvatinib, everolimus, temsirolimus, bevacizumab, axitinib, and sorafenib in combination with "Renal Cell Carcinoma." Adverse events of interest were bleeding complications specified by: site unspecified bleeding, site unspecified hemorrhage, hematoma, hemoptysis, hematuria, epistaxis, melena, hematochezia, hematemesis, hemothorax, and menorrhagia.

ClinicalTrials.gov was searched for additional information on bleeding incidence from the trials identified through the PubMed/Medline search. Bleeding events that were considered "Serious Adverse Events" by ClinicalTrials.gov were collected. The definition of "Serious Adverse Events" from ClinicalTrials.gov can be found in Table 1. Finally, corresponding authors were contacted for further information on bleeding incidence and clinical trial information. The reasons for contacting corresponding authors included clarifying doses used in the trials and inquiring about further bleeding or thrombocytopenia events that occurred.

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Table 1
Definitions of bleeding events included in article.

Type of Event	Definition
Grade 1 (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE), 2009	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE), 2009	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE), 2009	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE), 2009	Life-threatening consequences; urgent intervention indicated.
Grade 5 (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE), 2009	Death related to AE.
Serious Adverse Event (ClinicalTrials.gov) ClinicalTrials. gov., 2017	Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/ incapacity or result in a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.

2.2. Inclusion/exclusion criteria

Inclusion criteria consisted of: English language; articles published in the last 15 years; randomized control trials; and phase II, III, or IV clinical trials of systemic anti-cancer agents in mRCC. Articles were excluded if they did not include the incidence of bleeding events, only included bleeding incidence in one arm, used the study medication in all arms of the trial, or were duplicate trials as confirmed by comparison with previous searched articles.

2.3. Trial quality ranking process

Trial quality was determined using the Jadad ranking system (Jadad et al., 1996). This system ranks trials on a scale of 0–5, with zero indicative of least quality and five being highest quality. “High quality” is typically defined as a Jadad score of 3–5 (Jadad et al., 1996). The five-point score is determined by giving a point for each of the following characteristics: randomized, double-blinded, inclusion of withdrawals and dropouts, description of an appropriate randomization process for the study, and description of an appropriate double blinding process (Jadad et al., 1996). Additionally, one point may be deducted if the process of randomization is inappropriate or the process double blinding is inappropriate for each criterion, totaling a possible two-point deduction (Jadad et al., 1996).

2.4. Data extraction

After articles were selected using inclusion and exclusion criteria, data extraction was conducted independently by one investigator (MC). Variables extracted included: author, year of publication, line of therapy, ClinicalTrials.gov number, phase of study, study arm treatment, evaluable patients per arm, median age, median overall survival (OS), median progression-free survival (PFS), median duration of therapy, type of bleeding event, number of all-Grade bleeding events, number of Grade 3–4 bleeding events, deaths due to bleeding events, and incidence of thrombocytopenia. Serious bleeding adverse effects were also extracted from ClinicalTrials.gov.

2.5. Definitions of bleeding events

Multiple bleeding events were collected to determine incidence of bleeding with each medication. Table 1 illustrates types of bleeding and definitions of each bleed. From each clinical trial all-Grade, Grades 3–4, and death due to bleeding events were collected. These events are defined according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE). Each event is graded on severity with 0 being the least severe and 5 indicating death attributed to the adverse event. All-grade, Grades 3–4, and death due to bleeding events were collected to illustrate how often bleeding events occurred and how often severe events happened with each agent. Finally, we collected “Serious Adverse Events” attributed to bleeding from ClinicalTrials.gov. The definition per ClinicalTrials.gov can also be found in Table 1. These events were collected to give an up-to-date incidence of bleeding events seen in the trials, along with the most common type of severe bleeding event.

3. Results

3.1. Study selection

A total of 169 articles were screened for eligibility. Of these, 146 articles did not meet the inclusion criteria: 105 articles did not include the incidence of bleeding; 4 articles only reported bleeding incidence in one arm; 18 articles included the studied medication in all arms of the clinical trial; and 19 articles were deemed to be duplicate articles. A total of 23 articles were identified through screening that met the inclusion and exclusion criteria. These articles reported data from 16 clinical trials, the difference accounting for multiple articles published using data from the same clinical trial. Fig. 1 outlines the search process used to identify relevant articles.

3.2. Study characteristics

Of the 16 clinical trials identified, 2 studied pazopanib, 3 studied sunitinib, 1 studied cabozantinib, 1 studied lenvatinib, 4 studied everolimus, 1 studied temsirolimus, 3 studied bevacizumab, 2 studied axitinib, and 5 studied sorafenib. This included 2 phase II trials, and 14 phase III trials. Six studies used the agent as first-line therapy (Escudier et al., 2007a; Escudier et al., 2010; Motzer et al., 2007; Motzer et al., 2009; Rini et al., 2008, 2010; Motzer et al., 2013a; Hutson et al., 2013; Eisen et al., 2015), 8 as second-line therapy (Escudier et al., 2007a; Escudier et al., 2010; Motzer et al., 2007; Motzer et al., 2009; Rini et al., 2008, 2010; Motzer et al., 2013a; Hutson et al., 2013; Eisen et al., 2015; Yang et al., 2003; Escudier et al., 2007b; Motzer et al., 2008, 2010; Rini et al., 2011; Motzer et al., 2013b; Hutson et al., 2014; Choueiri et al., 2015; Motzer et al., 2015b), and 2 included both first-line and second-line treatment (Sternberg et al., 2010; Sternberg et al., 2013; Motzer et al., 2013c). Additional information about each trial is included in Table 2.

The majority of regimens in the identified trials were consistent with FDA-approved doses for use in mRCC (Table 2). The dosages used in 2 studies deviated from standard practice: one used bevacizumab 3 mg/kg IV every 2 weeks and bevacizumab 10 mg/kg every 2 weeks as monotherapy, and one used lenvatinib 24 mg orally daily (Yang et al.,