Cancer Letters 343 (2014) 156–160

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Targeted therapy in metastatic renal carcinoma

Jane Mattei, Rodrigo Donalisio da Silva, David Sehrt, Wilson R. Molina, Fernando J. Kim *

Chief of Urology, Denver Health Medical Center, 777 Bannock Street, Denver, CO 80204, United States

ARTICLE INFO

Article history:
Received 27 August 2013
Received in revised form 23 September 2013
Accepted 26 September 2013

Keywords:
Target therapy
Renal cell carcinoma
Metastatic disease
Renal tumor
Adjuvant treatment

ABSTRACT

Background: Advanced renal cell carcinoma is one of the most treatment-resistant malignancies to conventional cytotoxic chemotherapy. The development of new targeted therapy was result of understanding biological pathways underlying renal cell carcinoma. Our objective is to provide an overview of current therapies in metastatic renal cell carcinoma.

Methods: MEDLINE/PUBMED was queried in December 2012 to identify abstracts, original and review articles. The research was conducted using the following words: "metastatic renal cell carcinoma" and "target therapy". Phase II and Phase III clinical trials were included followed FDA approval. Total of 40 studies were eligible for review.

Conclusion: The result of this review shows benefit of these target drugs in tumor burden, increase progression-free and overall survival and improvement the quality of life compared with previous toxic immunotherapy, although complete response remains rare.

Published by Elsevier Ireland Ltd.

1. Introduction

Metastatic renal cell carcinoma is highly resistant to chemotherapy. Although a higher incidence of small renal masses are being detected, approximately one in three patients still present with metastases disease [1,2]. Immunotherapy including IL-2 and IFN-α had long been the main stay of treatment of advanced renal cell carcinoma (RCC) with responses only in a small subset of patients resulting in a 5-year survival of 6% [3,4]. Significant advances in the understanding of renal cell tumor biology have led to the development of molecular therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways resulting in significant improvement in overall survival and quality of life [1].

This aim of this systematic review is to provide a summary of contemporary and investigational therapies for the treatment of metastatic renal cell carcinoma.

2. Methods

2.1. Search strategy and study selection

The systemic review of targeted therapies in metastatic RCC was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was aimed at finding relevant studies and clinical trials from PUBMED/MEDLINE (1966–2013). Targeted therapies were identified by researching "target therapy and "metastatic renal cell carcinoma". The terms identified included names of following therapies; 'Sunitinib', 'Sorafenif', 'Pazopanib', 'Axitinib', 'Cediranib', 'Everolimus', 'Temsirolimus', 'Bevacizumab', and 'Erlotinib'

Study inclusion criteria included contemporary articles published after 2000, were published in English, reported data of the Phase II and III Clinical Trials and of outcomes following FDA approval, one reviewer identified all studies that appeared to fit the inclusion criteria for full review. Total of 40 studies were eligible for review (see Fig. 1).

2.2. Data extraction and analysis

Studies relevant to the targeted therapy of metastatic renal cell carcinoma were included. The following variables were extracted from each study: study name, period of the study, molecular targets of the drug, FDA approval status, and indication of treatment, recommended dosage of the drug, safety and efficacy of the drug. Efficacy was evaluated by the Overall survival (OS), progression free survival (PFS), and time to progression (TTP) as defined by the FDA Center for Drug Evaluation and Research. Safety was evaluated by the severity of adverse events defined by the Common Toxicity Criteria (CTC) (see Table 1).

3. Evidence synthesis

3.1. VEGF targeted therapies

Renal cell carcinomas are among the most vascularized of all solid tumors and angiogenesis is critical for tumor growth and progression. Vascular endothelial growth factor and its receptor-VEGF/VEGFR mediate VEGFR regulation of vessel permeability, endothelial cell activation, survival, proliferation, invasion and migration. Receptors for VEGFR and PDGFR exhibit tyrosine kinase activity and, upon ligand binding, activate downstream signaling pathways as the Raf/MEK/ERK [5]. Raf is a key in regulating endothelial cell survival, during angiogenesis, via effects on

* Corresponding author. Tel.: +1 303 436 6575.
E-mail address: fernando.kim@dhha.org (F.J. Kim).

0304-3835/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.canlet.2013.09.038

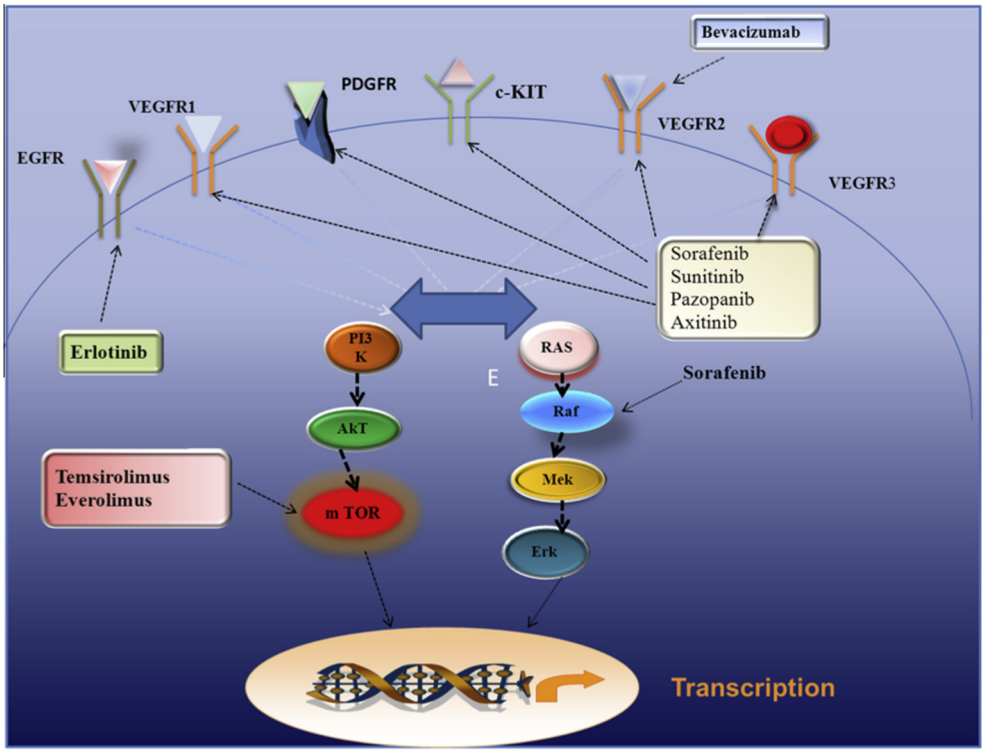

Fig. 1. Therapeutic biological pathways in renal-cell carcinoma.

intrinsic and extrinsic apoptosis pathways [6–8]. A number of drugs have been developed to target this pathway.

3.2. Sorafenib

Sorafenib was the first antiangiogenic multikinase inhibitor for mRCC approved by the FDA (2005). It is an oral multikinase inhibitor with activity against RAS family, VEGFR-1-3 and PDGFR 7. Sorafenib is considered a second line therapy and recommended dose is 400 mg twice a day.

The TARGET trial (Phase III) evaluated the efficacy of sorafenib vs. placebo in 903 patients who had failed previous standard therapy. 8 Interim analysis showed a significantly longer PFS with sorafenib compared to placebo (5.5 vs. 2.8 months; $p < 0.001$). Partial responses were reported in 10% of patients receiving sorafenib and in 2% of those receiving placebo ($p < 0.001$). The placebo patients were allowed to cross over at that time that sorafenib showed to reduce the risk of death. After 16 months after crossover, the overall survival time in the sorafenib treated cohort was 17.8 months compared with 15.2 months for the placebo group ($p < 0.146$). After censoring of the crossover patients, the estimated overall survival for the placebo-treated patients was 14.3 months. Common adverse events were skin rash/desquamation, hand-foot skin reaction, and fatigue; 9% of patients discontinued therapy, and no patients died from toxicity [7–9].

3.3. Sunitinib

Sunitinib soon followed and was approved by the FDA in 2006. Sunitinib also is an inhibitor of VEGFR1-3 and PDGFR. It has also direct antitumor effects on ligands which promotes the proliferation and differentiation of hematopoietic cells as the Fms-like tyrosine kinase 3 (FLT3), stem-cell factor receptor (c-KIT) [10,11]. Sunitinib is considered a primary option for the treatment of mRCC. It is orally administered with the recommended daily dose of 50 mg/day by a schedule 4/2.

The Phase III trial of sunitinib enrolled 750 patients and compared sunitinib to interferon. Sunitinib doubled progression-free survival (11 months vs. 5 months). The objective response rates were 47% and 12% for sunitinib and interferon-α, respectively ($p < 0.001$) and the median overall survival was 26.4 months for sunitinib and 21.8 months for interferon-alfa ($p = 0.051$) [12]. Moreover, a global expanded access Phase III study with 4564 patients was conducted to provide sunitinib on relatively unselected or trial-ineligible patients with brain metastases and with poor ECOG performance status. Results showed a median progression-free survival of 10.9 months and median overall survival of 18.4 months with similar overall survival in patients with and without prior cytokine therapy. Adverse events related with sunitinib included hypertension, fatigue, diarrhea and hand-foot syndrome, but none of these adverse events were graded with high severity. When applied Q-TWiST (quality-adjusted time without symptoms of disease progression or toxicity of treatment) score, sunitinib resulted better clinical efficacy and quality-of-life outcomes compared with IFN-alfa for mRCC patients [13].

3.4. Pazopanib

Pazopanib was approved by the FDA in 2009 and is a second generation of multi-target tyrosine kinase receptor. It is an orallyan orally bioavailable, multi-targeted TKI that inhibits the function of multiple receptor kinases including VEGFR1-3, RET and c-kit [14–16]. It is recommended as a first-line treatment and an option as a second line in previously cytokine-treated patients [17,18]. The drug is administered orally with 800 mg once daily.

The Phase III trial showed a significant improvement in PFS and RR in treatment-naive and cytokine-pretreated patients with advanced and/or metastatic RCC. Of 435 patients enrolled, the