Toxicities of Targeted Therapy and Their Management in Kidney Cancer

Giuseppe Di Lorenzoa,*, Camillo Portab, Joaquim Bellmunct, Cora Sternbergd, Ziya Kirkalie, Michael Staehlerf, Steven Joniaug, Francesco Montorsih, Carlo Buonerba

a Department of Endocrinology and Medical Oncology, Genitourinary Cancer Section, University Federico II, Napoli, Italy
b Medical Oncology, IRCCS San Matteo University Hospital Foundation, Pavia, Italy
c Medical Oncology, Service Hospital del Mar, Barcelona, Spain
d Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy
e Dokuz Eylul University, School of Medicine Inciralti-Izmir, Izmir, Turkey
f Department of Urology, University of Munich, Munich, Germany
g Oncologic and Reconstructive Urology, Department of Urology, University Hospitals Leuven, Leuven, Belgium
h Urology Division, San Raffaele University, Milan, Italy

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Abstract

Context: The therapeutic scenario for metastatic renal cell carcinoma (mRCC) has been evolving rapidly, with sunitinib, sorafenib, bevacizumab, everolimus, pazopanib, and temsirolimus being successfully tested and approved in a short period of time. Oncologists must be familiar with the management of toxicity that these biologic agents cause, as such toxicity is different from that of conventional chemotherapeutic agents.

Objective: To describe toxic effects associated with targeted therapy of mRCC and their proper management on the basis of currently available evidence.

Evidence acquisition: We conducted a systematic analysis of the literature on 15th October 2010 by performing a search of Medical Subject Headings (MeSH) on PubMed using the words sorafenib, sunitinib, bevacizumab, everolimus, pazopanib, or temsirolimus combined with the MeSH term kidney neoplasms. Consideration for inclusion was given to articles providing data concerning (1) incidence and grading and (2) management of targeted therapy–related toxic effects. A separate search was conducted on PubMed to retrieve meta-analyses using each drug name and the word meta-analysis.

Evidence synthesis: Hypertension, fatigue, bone marrow toxicity, skin toxicity, and gastrointestinal side-effects are common with the six targeted agents. Everolimus and temsirolimus are associated with immunosuppression, metabolic alterations, and interstitial pneumonitis, while sunitinib is associated with hypothyroidism. Recommendations for treating these conditions usually follow those for the general population because of the lack of experimental data in this setting (eg, for management of sunitinib-induced hypertension).

Conclusions: The treating oncologist should try to manage side-effects associated with targeted therapy using supportive and pharmacologic interventions. Severe toxicity requires external specialist consultation and treatment suspension and/or dose reduction. Experimental data about the management of targeted therapy–related toxicity in mRCC is lacking and required in this setting.

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* Corresponding author. Department of Endocrinology and Medical Oncology, Genitourinary Cancer Section, University Federico II, Napoli, Italy. Tel. +39 081 7463660; Fax: +39 081 2203147. E-mail address: giuseppedilorenzoncol@hotmail.com (G. Di Lorenzo).
1. Introduction

The therapeutic scenario for metastatic renal cell carcinoma (mRCC) has been evolving rapidly, with a plethora of pharmaceuticals showing effectiveness in several large, well-conducted phase 3 trials [1]. Six targeted agents have been approved in Europe, the United States, and other countries for specific subgroups of patients with mRCC [2]. As a first-line treatment, bevacizumab (Avastin®)—an anti–vascular endothelial growth factor (VEGF) monoclonal antibody—plus interferon and sunitinib (Sutent®)—a multi–tyrosine kinase inhibitor (TKI)—are recommended for good- and intermediate-risk patients. Pazopanib (Votrient®) is another multi-TKI that has been approved by the US Food and Drug Administration (FDA), the European Medicine Agency (EMA), and other countries for locally advanced or metastatic RCC. Temsirolimus (Torisel®), a mammalian target of rapamycin (mTOR) inhibitor, is recommended for first-line treatment in poor-risk patients. As a second-line treatment, sorafenib (Nexavar®), a TKI, is indicated after progression with cytokines or in cytokine unsuitable patients, while everolimus (Afinitor®) is recommended after progression with sorafenib and/or sunitinib [2] (Table 1).

These biologic agents present a toxicity profile that is very different from that of "conventional" chemotherapeutic agents. Their use requires in-depth knowledge of a large number of possible side-effects and drug interactions that have to be evaluated in light of patients' comorbidities and general health status. Urologic oncologists treating mRCC must be familiar with current therapeutic strategies for conditions such as hypertension, diabetes, and hyperthyroidism, which are reported with targeted agents.

Recommendations regarding the management of toxicity associated with sunitinib, sorafenib, and temsirolimus have been previously published [3]. The systematic analysis conducted for this review includes all biologic agents currently approved for mRCC. The best estimate for the incidence of treatment-emergent adverse events is presented on the basis of data from phase 3 and 4 trials along with the available evidence regarding their proper management. Side-effects particularly associated with targeted therapy are thoroughly described, together with flow charts about their identification and treatment.

2. Evidence acquisition

A systematic analysis of the literature was conducted on 15 October 2010 by performing a search of Medical Subject Heading (MeSH) terms on PubMed using the words sorafenib, sunitinib, bevacizumab, everolimus, pazopanib, or temsirolimus combined with the MeSH term kidney neo-plasms. Consideration for inclusion was given to articles providing data concerning (1) incidence and grading and (2) management of targeted therapy–related toxic effects. Selection criteria included articles written in English presenting data from phase 3 or phase 4 trials as well from other clinical studies specifically exploring selected toxic effects or toxicity in particular, clinically significant subsets of patients with mRCC. A separate search was conducted on PubMed to retrieve meta-analyses using each drug name and the word meta-analysis. No temporal limit was applied. Abstracts published by the American Society of Clinical Oncology and the European Society of Medical Oncology between 2005 and 2010 were also considered, but priority for inclusion was given to full, peer-reviewed papers.

Recommendations were retrieved from various authoritative sources, such as the National Comprehensive Cancer Network 2010 guidelines [4]; the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [5]; the European Society of Cardiology [6]; and the European Society of Hypertension [6]; and the European Association for the Study of Diabetes [7] as well as from manufacturers’ package inserts for the six drugs [8–13].

3. Evidence synthesis

3.1. Results of the systematic review

A total of 420, 319, 177, 51, 133, and 20 articles were considered for sunitinib, sorafenib, bevacizumab, everolimus,

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMA approval in KCa for—</th>
<th>FDA approval in KCa for—</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Advanced RCC when anticancer treatment with IFN-α or IL-2 has failed or cannot be used</td>
<td>Treatment of patients with advanced RCC</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>MRCC, a type of KCa that has spread to other organs</td>
<td>Treatment of advanced RCC</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Advanced or metastatic KCa in combination with IFN-α</td>
<td>Treatment of mRCC in combination with IFN-α</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Advanced RCC (KCa that has started to spread); used when the cancer has become worse</td>
<td>Treatment of patients with advanced RCC</td>
</tr>
<tr>
<td></td>
<td>during or after previous treatment with a medicine that targets VEGF</td>
<td>after failure of treatment with sunitinib or sorafenib</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Advanced RCC</td>
<td>Treatment of advanced RCC</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Advanced RCC; used in patients who have not received previous treatment or who have</td>
<td>Treatment of patients with advanced RCC</td>
</tr>
<tr>
<td></td>
<td>already been treated for their advanced disease with anticancer medicines called cytokines</td>
<td></td>
</tr>
</tbody>
</table>

EMA = European Medical Agency; KCa = kidney cancer; FDA = US Food and Drug Administration; RCC = renal cell carcinoma; IFN-α = interferon-α; IL-2 = interleukin-2; mRCC = metastatic renal cell carcinoma; VEGF = vascular endothelial growth factor.

* The European Medical Agency Web site (www.emea.europa.eu) and the US Food and Drug Administration Web site (www.fda.gov) were accessed 30 October 2010. According to EMA, “advanced” means that the cancer has started to spread.
<table>
<thead>
<tr>
<th></th>
<th>Sunitinib (n = 375) [14,15]</th>
<th>Sorafenib (n = 451) [16,17]</th>
<th>Bevacizumab by Rini (n = 266) [18,19]</th>
<th>Bevacizumab by Escudier (n = 327) [20,21]</th>
<th>Everolimus (n = 272) [22,23]</th>
<th>Temsirolimus (n = 209) [24]</th>
<th>Pazopanib (n = 290) [25]</th>
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<td></td>
<td>All grades</td>
<td>Grade 3–4</td>
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<tr>
<td>Fatigue</td>
<td>51</td>
<td>11</td>
<td>29</td>
<td>3</td>
<td>35</td>
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<td>Hypophosphatemia</td>
<td>31</td>
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<td>–</td>
<td>13</td>
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<td>–</td>
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<tr>
<td>Hyperlipasemia</td>
<td>56</td>
<td>18</td>
<td>41</td>
<td>12</td>
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<td><strong>Cardiovascular and respiratory toxicity</strong></td>
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<td>Hypertension</td>
<td>30</td>
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<td>17</td>
<td>4</td>
<td>9</td>
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<td>26</td>
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<td>Decline in LVF</td>
<td>13</td>
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<td>–</td>
<td>–</td>
<td>0</td>
<td>0</td>
<td>&lt;1</td>
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<tr>
<td>Bleeding</td>
<td>–</td>
<td>–</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>33</td>
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<tr>
<td>Thrombosis/embolism</td>
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<td>–</td>
<td>1</td>
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<td>3</td>
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<tr>
<td>Dyspnoea</td>
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<td>2</td>
<td>14</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>13</td>
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<tr>
<td>Pneumonitis</td>
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<td><strong>Bone marrow toxicity</strong></td>
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<td>Leukopenia</td>
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<td>8</td>
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<td>–</td>
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<tr>
<td>Neutropenia</td>
<td>77</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>8</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Lymphopenia</td>
<td>68</td>
<td>18</td>
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<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Anaemia</td>
<td>79</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>10</td>
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<tr>
<td>Thrombocytopenia</td>
<td>68</td>
<td>9</td>
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<td>–</td>
<td>2</td>
<td>0</td>
<td>6</td>
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<tr>
<td><strong>Gastrointestinal, hepatic, and renal toxicity</strong></td>
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<tr>
<td>Anorexia</td>
<td>34</td>
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<td>14</td>
<td>&lt;1</td>
<td>17</td>
<td>0</td>
<td>36</td>
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<tr>
<td>Nausea</td>
<td>44</td>
<td>3</td>
<td>23</td>
<td>6</td>
<td>–</td>
<td>7</td>
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<tr>
<td>Vomiting</td>
<td>24</td>
<td>4</td>
<td>16</td>
<td>6</td>
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<td>–</td>
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<tr>
<td>Diarrhoea</td>
<td>53</td>
<td>5</td>
<td>43</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>Proteinuria</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>15</td>
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<tr>
<td>Hypercreatininemia</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Hyperbilirubinemia</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>↑ ALT levels</td>
<td>46</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>↑ AST levels</td>
<td>52</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Dermatologic toxicity</strong></td>
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<tr>
<td>Mucositis</td>
<td>20</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>HSFR</td>
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<td>30</td>
<td>12</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>2</td>
<td>40</td>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

LVF = left ventricular failure; ALT = alanine aminotransferase; AST = aspartate transaminase.
The combination of sorafenib, temsirolimus, and pazopanib, respectively. The search of the six agents combined with the word meta-analysis provided a total of 89 results. According to the criteria described in the "Evidence acquisition" section, a total of 42 articles were included in the systematic review [14–55]. Twelve additional articles [56–67] were included in the review article to comply with comments by coauthors and reviewers. Toxic side-effects in reviewed articles were graded according to the Common Toxicity Criteria v.3.0 of the US National Cancer Institute [68] if not specified otherwise.

3.2. Treatment-related toxicity and its management

3.2.1. Constitutional toxicity

Constitutional symptoms associated with targeted therapy include fatigue, asthenia, infections, fever, weight loss, chills, and influenza-like illness. Of these, fatigue is a prominent, commonly reported adverse event, with an incidence ranging from 14% to 51% for any grade and an incidence of up to 11% for grade 3–4 events in the phase 3 trials (Table 2). In the expanded access protocols, grade 3–4 fatigue was reported in 8% of 4564 mRCC patients treated with sunitinib [26] and in 4.5% of 2504 mRCC patients treated with sorafenib [27]. Cancer-related fatigue is perceived by patients as a chronic feeling of tiredness or general lack of energy not alleviated by rest. Besides cancer treatments and the underlying cancer illness, fatigue can be caused or aggravated by a variety of factors, such as anemia; pain; depression; anxiety; sleep disorders; nutritional status; medication side-effects; and functional impairment of the heart, lungs, kidney, liver, nervous system, and endocrine system [4]. Fatigue can also be exacerbated by muscle loss, which was found to be associated with sorafenib treatment [28].

Onset of fatigue or its worsening could indicate clinical disease progression. Compilation of a daily diary, with self-assessment of fatigue, is useful for monitoring the effectiveness of medical intervention and recognising moments of maximum energy during the day. As a general rule, patients should be encouraged to save physical and mental energy (eg, by delegating tasks, through labour-saving devices) and dedicate themselves to social and enjoyable activities. It is essential to limit daylight sleeping to avoid affecting nighttime sleep quality. Nonpharmacologic interventions include rehabilitation, massage therapy, cognitive behavioural therapy, regular physical activity, and exercise [4]. Administration of psychostimulants such as methylphenidate and erythropoesis-stimulating agents in anaemic patients is the only pharmacologic intervention for grade 3–4 events in the phase 3 trials (Table 2). The incidence with pazopanib which occurred in 14% of mRCC patients enrolled in the phase 3 trial (Table 2). The incidence with pazopanib appears to be lower (<10%) [25].

Although hypothyroidism was not mentioned among the side-effects in the phase 3 and 4 trials of sorafenib, a 67.7% incidence was reported in 69 Japanese mRCC patients, with 5.8% of the study population requiring thyroid hormone replacement [58]. In a retrospective analysis of 73 mRCC patients treated with sunitinib, 85% of patients showed some abnormalities in thyroid function tests, 70% had elevated thyroid-stimulating hormone (TSH) levels, and 68% showed decreased triiodothyronine levels [29]. Increased serum thyroid-stimulating hormone (TSH) levels, a decrease in FTI with elevated TSH levels. Of the 42 patients with mRCC, 33% had elevated TSH levels but did not require administration of exogenous thyroid hormones, and an equal proportion of patients presented with hypothyroidism and required thyroid hormone substitution therapy.

Exogenous thyroid hormones should be administered in symptomatic patients with normal free thyroxine (FTI)
levels but elevated TSH levels (threshold value: 10 mIU/l) and in patients with overt hypothyroidism, as shown by the algorithm reported in Fig. 1. The specific timing for assessment of thyroid function on days 1 and 28 of the 6-wk cycle was selected, because the peak in TSH levels was reported to occur after 4 wk of treatment with sunitinib [30]. Screening for hypothyroidism as recommended in the drug package insert can be conducted for pazopanib in a similar way, with thyroid assessments approximately every 8 wk.

Unfavourable metabolic alterations, including hyperglycaemia, hypertriglyceridaemia, and hypercholesterolaemia, are common with mTOR inhibitors as well with pazopanib. In the phase 3 trials, 41% of patients treated with pazopanib presented with grade 1–2 hyperglycaemia, while the incidence of grade 3–4 hyperglycaemia was 15% and 11% with everolimus and temsirolimus, respectively (Table 2). Patients with untreated diabetes and/or dyslipidaemia at the initial assessment should be referred to a specialist. According to the European Association for the Study of Diabetes [7], diabetes should be initially approached with dietetic and lifestyle modifications. Glycosylated haemoglobin levels should be assessed as often as every 12 wk, while self-assessment of fasting and postprandial glucose levels on a daily basis is mandatory for patients on insulin therapy and beneficial for all diabetic patients. Many oral agents are currently approved for type 2 diabetes, with several conditions favouring or contraindicating the use of specific pharmacologic classes. Biguanides such as metformin (500–1500 mg/d) and glitazones such as pioglitazone (15–45 mg/d) are used to improve insulin sensitivity. Sulphonylureas such as glimepiride (1–6 mg/d) can compensate for insulin deficiency.

Sulphonylureas and biguanides are contraindicated in case of impaired kidney function; glitazones, biguanides, and α-glucosidase inhibitors are contraindicated in cases of impaired liver function; biguanides and glitazones are contraindicated in cases of impaired cardiopulmonary function. As a general rule, pharmacologic treatment should start with an oral insulin-sensitizer such as metformin or an α-glucosidase inhibitor. If acceptable glycaemic control (fasting glycaemia <110, postprandial glycaemia <140, glycated haemoglobin levels <6.5) is not accomplished, sulphonylureas can be introduced. Insulin-sensitizer glitazones can be used as part of double or triple oral combination therapy. The novel agent sitagliptin (100 mg/d), which increases insulin secretion by slowing
randomised controlled trials (RCT; Table 2). Three meta-
with an incidence ranging from 9% to 30% in the reviewed
7.1% for bevacizumab[33], respectively, in the subgroup of
types of cancer found an incidence of grade 3–4 hyperten-
ction of 8.3% for sunitinib[31], 6.5% for sorafenib[32], and
hypertension [60]. Hypertension of any grade was reported
and physical activity[5]. See Table 3 for the management of
metabolic toxicities. No dose reduction or treatment
suspension is specified in the product monographs with
regard to metabolic toxicity.

3.2.4. Cardiovascular toxicity
Careful cardiovascular monitoring as well as prophylactic cardiovascular treatment are essential and may allow con-
tinuation of aggressive therapy for the underlying cancer
[59]. The most relevant side-effect in clinical practice is
hypertension [60]. Hypertension of any grade was reported
with an incidence ranging from 9% to 30% in the reviewed
randomised controlled trials (RCT; Table 2). Three meta-
analyses of phase 2, 3, and 4 trials conducted in various
types of cancer found an incidence of grade 3–4 hyperten-
sion of 8.3% for sunitinib [31], 6.5% for sorafenib [32], and
7.1% for bevacizumab[33], respectively, in the subgroup of
mRCC patients. The proper management of hypertension is
fundamental importance in mRCC patients, but it can
only be extrapolated from guidelines available for the
general population because of the lack of experimental data
in this setting [5].

The aim of reducing long-term cardiovascular mortality
might be considered less imperative in a population with
reduced life span such as mRCC patients. On the contrary:
Avoiding acute, life-threatening events as well as dose
reduction or treatment suspension is the main goal of
antihypertensive treatment in this setting. Behavioural and
pharmacologic interventions should pursue a blood pres-
sure (BP) lower than 140/90 mm Hg. Patients at high or very
high risk, as defined by the criteria reported in Table 4,
are preferably managed by a specialist in view of their multiple
risk factors and/or comorbidities. Antihypertensive agents
should be selected according to the individual patient’s
comorbidities, drug interactions, and contraindications. As
an example, thiazides (hydrochlorothiazide 12.5–100 mg)
and antialdosterone diuretics (spironolactone 100–400 mg/
d), beta-blockers (atenolol 50–100 mg/d), angiotensin-
converting enzyme (ACE) inhibitors (lisinopril 5–40 mg/
d), and angiotensin II receptor blockers (losartan 50–
100 mg/d) have positive effects independently on BP
decrease in patients suffering from heart failure. Patients
with angina pectoris can benefit from dihydropyridine
calcium antagonists (amlodipin 5–10 mg/d) as well as beta-
blockers. The use of ACE inhibitors and angiotensin II
receptor blockers is also advantageous in kidney failure, but
requires caution in patients with bilateral renal artery
stenosis. A simple flow chart of hypertension management
is provided in Fig. 2.

| Initial approaches | Metformin (500-1500 mg / day) or acarbose (150-300 mg/die) | Statins (atorvastatin, 10-80 mg / day) are the first-choice drugs | Treated hypercholesterolemia as long as triglyceridaemia is below 500 mg / dl |
| Subsequent approaches | Add sulphonylureas such as glimepiride (1-6 mg/day) or sitagliptin (100 mg /day) | Add a bile acid sequestrant (cholestyramine, 4-24 g / day or nicotinic acid in fixed combination with laropiprant, Tredaptive®, 2000 mg nicotinic acid and 40 mg laropiprant/day) | Add Tredaptive, 2000 mg nicotinic acid and 40 mg laropiprant/day |
| If severe toxicity or previous approaches fail | Start fibrates (gemfibrozil, 900-1200 mg/die, avoid concomitant use with statins) | Specialist consultation | |

Table 4 – Conditions identifying patients at high and very high cardiovascular risk. Reproduced with permission of Oxford University Press [6]

- BP ≥180 mm Hg systolic and/or ≥110 mm Hg diastolic
- High systolic BP (>160 mm Hg) with low diastolic BP (<70 mm Hg)
- Diabetes mellitus
- Metabolic syndrome
- Three cardiovascular risk factors
- Established cardiovascular or renal disease
- One or more of the following subclinical organ damages:
  - Electrocardiographic (particularly with strain) or echocardiographic (particularly concentric) left ventricular hypertrophy
  - Ultrasound evidence of carotid artery wall thickening or plaque
  - Increased arterial stiffness
  - Moderate increase in serum creatinine
  - Reduced eGFR or creatinine clearance
  - Microalbuminuria or proteinuria

BP = blood pressure; eGFR = estimated glomerular filtration rate.
VEGF-directed agents can alter the haemostatic balance by interfering with the integrity of the endothelial cells, with decreased production of nitric oxide and alteration of membrane lipids. They have been associated with both coagulative and bleeding disorders. Meta-analyses have shown that bevacizumab was significantly associated with an increased risk of arterial thromboembolism [34] and venous thromboembolism [35] as well as bleeding events [36] in mRCC patients with respect to controls. Sorafenib and sunitinib were also associated with an increased risk of arterial thromboembolic events [37] and bleeding events [38] in patients with mRCC with respect to controls. A retrospective study of patients with metastatic RCC treated with sorafenib or sunitinib showed an incidence of 7% (5 of 67) fatal intracerebral haemorrhage, with four of five patients presenting with brain metastasis [39]. This increased risk should be carefully monitored with a thorough medical history, frequent clinical examinations, and immediate investigation of any suspicious symptoms. Grade 2–4 thrombotic or bleeding events require treatment suspension and appropriate therapy until recovery to grade 1.

The incidence of left ventricular cardiac dysfunction (LVCD) reported with sunitinib in the phase 3 trial was 13%, with 3% of patients experiencing grade 3 events (Table 2). The expanded access trial of sunitinib reported cardiac failure of any grade in <1% of patients, although a baseline cardiac evaluation was not included in the protocol [26]. Di Lorenzo et al reported grade 3 LVCD and/or congestive heart failure in two patients with mRCC who were treated with sunitinib. The use of corticosteroids as a prophylactic measure was not considered in these trials, as the benefit of corticosteroids in preventing LVCD was not established.

Table 5 – Clinical management of noninfectious pneumonitis

<table>
<thead>
<tr>
<th>Grade 1 Asymptomatic, radiographic findings only</th>
<th>Grade 2 Symptomatic, not interfering with ADL</th>
<th>Grade 3 Symptomatic, interfering with ADL, oxygen indicated</th>
<th>Grade 4 Life-threatening; ventilation support indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention Continue everolimus</td>
<td>Depending on severity of symptoms:</td>
<td>Interrupt everolimus.</td>
<td>Interrupt everolimus.</td>
</tr>
<tr>
<td>No change in dose</td>
<td>• Consider everolimus dose interruption/reduction.</td>
<td>• Consult a pulmonologist.</td>
<td>• Consult a pulmonologist.</td>
</tr>
<tr>
<td></td>
<td>• Consult a pulmonologist.</td>
<td>• Run diagnostics to exclude infectious causes.</td>
<td>• Run diagnostics to exclude infectious causes.</td>
</tr>
<tr>
<td></td>
<td>• Consider corticosteroids.</td>
<td>• Corticosteroids if infectious cause is excluded.</td>
<td>• Corticosteroids if an infectious cause is excluded.</td>
</tr>
<tr>
<td></td>
<td>• Restart at reduced dose when grade ≤1, and consider re-escalation.</td>
<td>• Hold treatment until recovery to grade 1; may restart within 2 wk at a reduced dose (by 1 level) if there is evidence of clinical benefit.</td>
<td>• Discontinue permanently.</td>
</tr>
<tr>
<td></td>
<td>• If no recovery to grade ≤1, discontinue everolimus.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADL = activities of daily living.
failure in 12 of 175 mRCC patients treated with first-line sunitinib [40]. Although there is no general agreement on this issue, these findings suggest that echocardiographic assessment of left ventricular ejection fraction (EF) should be performed every cycle for the first four cycles and then every three cycles for patients at high risk for associated risk factors. Patients not presenting with a history of coronary artery disease and/or hypertension can have their EF assessed every three cycles. Consultation with a specialist is appropriate for any grade of LVCD for supportive therapy.

3.2.6. Bone marrow toxicity

Overall, biologic agents tend to cause haematologic toxicity less frequently with respect to conventional chemotherapy agents. Anaemia occurred in 79% of patients treated with sunitinib and in 45–92% of patients treated with mTOR agents. Anaemia occurred in 79% of patients treated with sorafenib and sunitinib. Major problem of therapy-associated anaemia is that radio- graphic evaluation may be misleading and misinterpreted as progressive pulmonary disease with new nodular metastatic lesions. Thus, any new small lesions in the lung should be carefully regarded for the presence of pneumoni- tis rather than progressive disease, especially in patient on mTOR inhibitors.

Thoracic radiographic assessments, performed every 8 wk, in 274 patients receiving everolimus enrolled in the RECORD-1 phase 3 trial were prospectively analysed by blinded, central review. Interstitial pneumonitis was suspected in 13.5% of patients, but only 3.6% of them had grade 3 events (which are those interfering with daily living or with oxygen required; Table 5) [41]. All patients treated with mTOR inhibitors should be warned to promptly report symptoms such as dyspnoea or cough. Spirometry, with determination of diffusive capacity of CO, and a thoracic CT scan should be conducted every 12 wk.

If noninfectious pneumonitis is diagnosed on the basis of clinical and radiologic findings, treatment suspension or dose reduction as well as medical intervention vary according to the severity of the condition. Table 5 describes in detail the recommendations of this panel for management of interstitial pneumonitis according to the severity of clinical manifestations.

3.2.7. Gastrointestinal, liver, and kidney toxicity

Anorexia, nausea, vomiting, and diarrhoea are frequent side-effects of targeted agents but are usually mild and rarely caused treatment discontinuation in the phase 3 trials (Table 2). Symptomatic medications include loperamide (2–16 mg/d) for diarrhoea, metoclopramide (10–20 mg/d) and ondansetron (8–32 mg/d) for nausea and/or vomiting, and megestrol acetate (160–800 mg/d) for anorexia. Gastrointestinal perforation is a rare but life-threatening event associated with bevacizumab (risk ratio [RR] in mRCC patients: 5.67; confidence interval [CI]: 0.66–48.2) [42] and warrants treatment discontinuation. Hepatic toxicity is frequently associated with targeted agents and is a class effect seen with VEGF receptor inhibitors such as sunitinib and pazopanib. About half of the patients exposed to these two agents showed elevated transaminases, and about one-fourth of them showed elevated bilirubin levels (Table 2). Antioxidant substances, such as N-acetylcysteine (600 mg/d) or glutathione (600–1200 mg/d) might helpful in managing hepatotoxicity.

One meta-analysis found that sunitinib was associated with an increased risk of renal dysfunction (RR: 1.36; 95% CI, 1.20–1.54, p < 0.001) [31]. A grade 1–2 rise in creatinine
levels was rather common in the phase 3 trials, especially in patients treated with sunitinib and everolimus (Table 2), but does not warrant treatment interruption or dose reduction, as biologic agents are rarely affected by kidney failure. Treatment should be interrupted for drug-induced grade 3–4 hypercreatininemia, which is very rare with all targeted agents (≤1%), and restarted at a lower dose once severe toxicity has resolved. Severe proteinuria occurred in 7–15% of patients treated with bevacizumab and requires treatment discontinuation with possible readministration. A meta-analysis of RCTs in various types of cancer found that bevacizumab was associated with a significantly increased risk of proteinuria (RR: 2.2 with the 10–15-mg/kg biweekly dose; 95% CI, 1.6–2.9) [43]. As a general rule, kidney and hepatic grade 1–2 toxicities require supportive measures but unlike grade 3–4 toxicity do not mandate treatment suspension. Dose reduction and treatment interruption with regard to hepatic and renal toxicity are detailed in Table 6.

3.2.8. Skin and mucosal toxicity

Up to 40% of patients treated with sorafenib and sunitinib presented with some form of skin or mucosal toxicity in the phase 3 trials (Table 2). Hand–foot skin reaction (HFSR) is the most prominent skin side-effect; its symptomatic manifestations typically include paresthesia, tingling, burning, painful sensations on the palms and soles and manifestations typically include paresthesia, tingling, burning, painful sensations on the palms and soles and sensitivity to hot objects [44]. HFSR occurred in 24% and 19% of the population of the expanded access trials on sorafenib [27] and sunitinib [26], respectively, although the incidence of severe events was greater with sorafenib than with sunitinib (10% vs 6%). Results from one meta-analysis indicated that high-grade, sorafenib-induced HFSR was less frequent in mRCC patients than in non-mRCC patients (4.7%; 95% CI, 2.8–7.8 vs 7.8%; 95% CI, 6.5–9.4) [45]. One observational study [44] prospectively evaluated the incidence of skin toxicity in 85 consecutive mRCC patients; 43 of them received sorafenib, while the remaining 42 were on placebo. In the sorafenib arm, 60% of patients presented with HFSR, and 63% of patients presented with facial and scalp erythematous eruption, although the incidence of grade 3–4 HFSR was only 5%, which is consistent with that reported in the expanded access trial [27]. Serious events did not occur in the placebo group. HFSR lesions presented as tender and scaling, with a peripheral halo of erythema and yellowish and hyperkeratotic plaques or callous-like blisters localised to areas of pressure. It is interesting to note that 54% of patients showed hyperkeratosis, which is not common with other agents like sunitinib and can be treated with urea-based keratolytic agents. In contrast, sunitinib-induced HFSR is typically associated with desquamation. Effective management of HFSR can begin prior to treatment initiation with sorafenib or sunitinib, as reported in Table 7. Patients should be advised to remove any preexisting hyperkeratotic areas or calluses.

Grade 1–2 skin rashes are managed with moisturising creams and topical hydrocortisone creams. Grade 3–4 skin rashes can be managed with low-dose oral prednisone (10–25 mg/d) and require treatment suspension until recovery to grade 1. Severe HFSR or rash should prompt consultation with a dermatologist. Alopecia, body hair loss, scalp dysesthesia, and subungual splinter haemorrhages were also frequently reported with sorafenib [44] and tended to resolve spontaneously.

3.3. Toxicity in particular subsets of patients

3.3.1. Pretreated patients

Everolimus is the only targeted agent specifically approved after failure of sunitinib or sorafenib or both, while mRCC populations enrolled in the other phase 3 trials had not been pretreated with other targeted agents. A phase 2 trial [46] of sorafenib in 52 mRCC patients pretreated with sunitinib showed a higher incidence of hypertension (27%), fatigue (34%), diarrhoea (48%), nausea/vomiting (48%), and rash (40%) than reported in the phase 3 trial in cytokine-refractory patients, and an even higher incidence of hypertension (36%) was reported in a similar phase 2 trial [47] on sorafenib in 48 patients pretreated with bevacizumab or sunitinib. The study by Garcia et al [47] also reported a considerably higher incidence of grade 3–4 fatigue (18% vs 3.8%) and grade 3–4 HFSR (31% vs 3.8%) than the study by Di Lorenzo et al [46]. The greater incidence of severe HFSR might be connected with prior exposure to bevacizumab [47]. Grade 3–4 neutropaenia was a rather frequent event in the cohort pretreated with sunitinib only (15.4%) [46] as well as 34 patients treated with sorafenib after sequential therapy with sunitinib and an mTOR inhibitor (8.8%) [48], but such events were not reported in patients pretreated with either sunitinib or bevacizumab [47].

The safety of another agent approved for first-line treatment, temsirolimus, was evaluated in a retrospective study of 87 patients who had been pretreated with sunitinib, sorafenib, or bevacizumab for the most part. Noninfectious pneumonitis was observed in 10% of patients, but only three of them required hospital admission for investigation and supportive care. Hyperglycaemia occurred in 27% of patients de novo, while 6% of patients with preexisting diabetes experienced a worsening of glycaemic control. This study showed that temsirolimus is safe after failure with VEGF-directed agents, with no unexpected side-effects [49].

3.3.2. Elderly patients

To the best of our knowledge, specific toxicity and efficacy analysis of targeted agents in elderly patients is currently available for sorafenib only. Both the phase 3 trial and the expanded access trial on sorafenib showed that the safety profile in elderly patients (≥70 yr of age) did not significantly differ from that of younger mRCC patients [50,51]. In the phase 3 trial, older patients on sorafenib (≥70 yr of age) showed an increased incidence of grade 3 (40.0% vs 29.4%) and grade 4 (5.7% vs 7.3%) events over younger patients, but these differences were not statistically significant. In contrast, differences in the rate of treatment discontinuation (21.4% vs 8.1%; p = 0.0015) and the incidence of grade 3–5 cardiovascular events (5% vs 0%; p = 0.0020) were statistically different in favour of younger patients. In the expanded access trial, the only statistically significant difference in severe toxicity was reported for grade 3–4 fatigue, which was
<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended schedule in mRCC</th>
<th>Recommended dose modifications</th>
<th>Warnings and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sunitinib [8]</strong></td>
<td>50 mg orally once daily, with or without food</td>
<td>To manage toxicity, dose ↓ or ↑ in 12.5-mg steps. To manage drug interactions, consider dose ↓ to 37.5 mg with strong CYP3A4 inhibitors. Consider dose ↓ to 87.5 mg with strong CYP3A4 inhibitors.</td>
<td><strong>Hepatotoxicity:</strong> Temporarily discontinue for grade 3–4 hepatotoxicity until recovery to grade 1. <strong>Cardiac ischaemia, infarction, or haemorrhage:</strong> Consider to discontinuing temporarily or stopping sorafenib. <strong>Skin toxicity, including HFSR:</strong> If grade 2 with no improvement within 7 d or at the second or third occurrence, temporarily discontinue sorafenib, then</td>
</tr>
<tr>
<td><strong>Sorafenib [9]</strong></td>
<td>400 mg orally twice daily without food (at least 1 h before or 2 h after a meal)</td>
<td>To manage toxicity, dose ↓ to 400 mg/d, then ↓ to 400 mg every other day. To manage drug interactions, consider dose ↓ with strong CYP3A4 inhibitors (no available data). For hepatic or renal impairment, no dose modification is required.</td>
<td><strong>Bleeding and arterial thrombotic events:</strong> Monitor and treat appropriately. <strong>Hypertension:</strong> Initiate antihypertensive therapy;</td>
</tr>
<tr>
<td><strong>Bevacizumab [10]</strong></td>
<td>10 mg/kg IV every 2 wk with IFN-α (9 MU subcutaneously three times per week). Duration of first infusion: 90 min. Duration of second infusion: 60 min (if the first infusion is tolerated). Duration of subsequent infusions: 30 min (if infusion over 60 min is tolerated)</td>
<td>No dose modification is recommended.</td>
<td><strong>Gastrointestinal perforation, fistula formation involving an internal organ OR wound dehiscence and wound healing complications requiring medical intervention OR serious hemorrhage OR severe arterial thromboembolic events</strong></td>
</tr>
<tr>
<td><strong>Everolimus [11]</strong></td>
<td>10 mg orally every day</td>
<td>To manage toxicity, dose ↓ to 5 mg/d. To manage drug interactions, dose ↓ to 20 mg/d or ↓ to 5 mg/d or ↓ to 12.5 mg/wk with strong CYP3A4 inhibitors. Avoid grapefruit juice. For hepatic impairment (bilirubin over ULN and &lt; 1.5 × ULN or AST under ULN but bilirubin at or under ULN), use 15 mg/wk. For hepatic impairment (bilirubin &gt; 1.5 × ULN), do not administer everolimus.</td>
<td><strong>Noninfectious pneumonitis:</strong> If asymptomatic, continue everolimus with no dose modification. If moderate, temporarily discontinue and ↓ dose. If severe, stop everolimus. <strong>Infections:</strong> Consider temporary discontinuation. <strong>Allergic reactions:</strong> Administer prophylactic IV diphenhydramine 25–50 mg (or similar antihistamine) 30 min before temsirolimus. Administer in 60-min if there are hypersensitivity reactions during 30-min infusions. <strong>Haematologic toxicity:</strong> If grade 3–4 neutropenia or</td>
</tr>
<tr>
<td><strong>Temsirolimus [12]</strong></td>
<td>25 mg IV infused over 30–60 min every week</td>
<td>To manage toxicity, dose ↓ to 20 or 15 mg/wk. To manage drug interactions, dose ↓ to 50 mg/wk with strong CYP3A4 inhibitors or ↓ to 12.5 mg/wk with strong CYP3A4 inhibitors. Avoid grapefruit juice.</td>
<td><strong>Hepatotoxicity:</strong> AST, ALT, bilirubin every 4 wk for at least the first 4 mo. <strong>If isolated ALT, ALT &gt;3 × ULN, and &lt;8 × ULN:</strong> Continue pazopanib, with weekly monitoring of ALT and AST until back to grade 1 or baseline. If isolated ALT</td>
</tr>
<tr>
<td><strong>Pazopanib [13]</strong></td>
<td>800 mg orally once daily without food (at least 1 h before or 2 h after a meal)</td>
<td>To manage toxicity, dose ↓ to 400 mg/d, then ↓ to 400 mg every other day. To manage drug interactions, dose ↓ to 400 mg with strong CYP3A4 inhibitors. Do not administer with strong CYP3A4 inducers. For moderate baseline hepatic impairment, use 400 mg/d. For severe baseline hepatic impairment, do not administer pazopanib.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6 – Summary of the package inserts**

- **Sunitinib**
- **Sorafenib**
- **Bevacizumab**
- **Everolimus**
- **Temsirolimus**
- **Pazopanib**
Table 6 (Continued)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>stop for severe or uncontrolled hypertension.</td>
<td>resume when back to grade 1. If grade 3 at first or second occurrence, temporarily discontinue sorafenib, then resume when back to grade 1 at full dose. If grade 2 at the fourth occurrence or grade 3 at the third occurrence, stop sorafenib.</td>
<td>OR hypertensive crisis or hypertensive encephalopathy OR reversible posterior leukoencephalopathy syndrome or nephrotic syndrome: Stop bevacizumab. At least 4 wk prior to elective surgery or severe hypertension not controlled with medical management or moderate to severe proteinuria pending further evaluation or severe infusion reactions: Temporarily discontinue bevacizumab.</td>
<td>Vaccinations: Avoid live vaccines. Wound healing complications: Avoid everolimus in the perioperative period.</td>
<td>grade 2–4 thrombocytopenia, temporarily discontinue temsirolimus, then dose when resuming. Noninfectious pneumonitis: Consider discontinuation and/or steroid use. Any grade 3–4 adverse event: Discontinue until recovery to grade ≤2.</td>
<td>or AST &gt;8 x ULN, interrupt until back to grade 1 or baseline, then reduce the dose. If ALT elevations &gt;3 x ULN recur, stop pazopanib. If ALT &gt;3 x ULN and bilirubin &gt;2 x ULN, stop pazopanib. QT prolongation: Monitor electrolytes and ECG.</td>
</tr>
<tr>
<td>Hypothyroidism: Monitor thyroid function. LVD: Stop for CHF, temporarily discontinue or reduce dose if no clinical evidence of CHF but EF &lt;50% and &gt;20% below baseline. QT prolongation: Monitor electrolytes and ECG.</td>
<td>Hypertension: Initiate antihypertensive therapy; stop for severe or uncontrolled hypertension.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† levels of anti-cancer agent for concomitant administration of—
CYP3A4 inhibitors CYP3A4 inducers CYP3A4/Pgp inhibitors CYP3A4 inhibitors CYP3A4 inhibitors

‡ levels of anticancer agent for concomitant administration of—
CYP3A4 inhibitors CYP3A4 inducers CYP3A4/Pgp inhibitors CYP3A4 inhibitors CYP3A4 inhibitors

Concomitant administration of anticancer agent † levels of—
Substrates of CYP2B6, CYP2C8, UGT1A1 (irinotecan), docetaxel, or doxorubicin Increase of AUC of drugs metabolised by Pgp, CYP3A4, and CYP2D6 is unlikely. CYP3A4, CYP2C8, and CYP2D6 weekly inhibited

mRCC = metastatic renal cell carcinoma; IV = intravenous; CYP3A4 = cytochrome P450 3A4; ULN = upper limit of normal; AST = aspartate aminotransferase; LVD = left ventricular dysfunction; CHF = congestive heart failure; EF = ejection fraction; ECG = electrocardiogram; ALT = alanine aminotransferase; Pgp = P-glycoprotein; AUC = area under the curve.
more frequent in older patients (7% vs 4%; \( p = 0.0021 \)). Although there was no statistically significant difference in the rate of dose reductions, older patients more frequently discontinued treatment because of adverse events (13% vs 8%; \( p = 0.0001 \)).

In conclusion, current existing data demonstrate the safety of sorafenib in the elderly population (>70%), with a possible small increased risk of severe cardiovascular events. Data for other targeted agents are missing.

### 3.3.3. Patients at risk for drug interactions

All targeted agents are metabolized by cytochrome P450 3A4 (CYP3A4). Strong and moderate CYP3A4 inhibitors can increase blood levels of the active anticancer agent except for sorafenib. Conversely, strong CYP3A4 inducers can reduce blood levels of the active anticancer agent. Patients should be warned to avoid consumption of grapefruit juice because of its inhibition of CYP3A4 (Table 8).

In view of the great potential for drug interaction, possibly causing decreased efficacy or increased toxicity, a complete medical history of patients treated with targeted agents should include a detailed analysis of all concomitant medications. Clinicians and patients must be well aware that unconventional pharmacologic agents, such as the “scorpion venom” from Cuba that has currently gained in popularity, do have the potential to influence CYP3A4 metabolism, as occurs for other unconventional medications, such as St. John’s wort or even foods such as grapefruit juice. Variations in the dose can be prudently considered in order to manage drug interactions, as reported in Table 6.

### 3.3.4. Patients treated with surgery and perioperative targeted therapy

Although neoadjuvant or adjuvant biologic therapy is still experimental, data about the perioperative safety of targeted agents in mRCC are available for sunitinib, sorafenib, and bevacizumab. One retrospective evaluation of 44 mRCC patients treated with upfront targeted therapy, including sunitinib (15 patients), bevacizumab (17 patients), and sorafenib (12 patients) versus a matched cohort of 58 patients treated with upfront surgery showed no statistically significant difference in the incidence of surgical complications [52]. In a phase 2 trial of neoadjuvant bevacizumab in mRCC [53], 42 patients underwent cytoreductive nephrectomies 4 wk after the last dose of bevacizumab, administered for 8 wk (10 mg/kg every 14 d).

### Table 7 – Recommendations for treatment of skin toxicity (modified from Bhojani et al [3])

<table>
<thead>
<tr>
<th>Initial nonpharmacologic measures</th>
<th>Pharmacologic interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash/desquamation</td>
<td>Moisturizing cream twice daily</td>
</tr>
<tr>
<td>Antidandruff shampoo</td>
<td>Grade 1–2: Hydrocortisone 1% cream</td>
</tr>
<tr>
<td>Loose clothing</td>
<td>Grade 3: Prednisone 25 mg orally daily for 2 d, then 10 mg orally four times a day for 7–14 d</td>
</tr>
<tr>
<td>Avoidance of direct sunlight, detergents, antibacterial soaps, alcohol-based perfumed lotion</td>
<td>Grade 4: Dermatology referral</td>
</tr>
<tr>
<td>Use sun protection of at least 30 SPF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>HFSR</td>
<td>Manicure and pedicure before and during treatment (especially in patients with comorbidities, such as diabetes). Use appropriate tools (e.g., a pumice stone) to aid in callus removal. During treatment, use shock absorbers for pressure points, sandals, thick cotton gloves and/or socks. Wear well-padded but nonconstrictive footwear; protect tender areas; do not walk barefoot. Avoid warm and/or hot water or objects; tight-fitting shoes; or other items that may rub, pinch, or cause friction in affected areas. Apply an alcohol-free moisturizer immediately after bathing. Corticosteroids have no proven efficacy. Delay and adjust treatment if grade 3–4 toxicity occurs.</td>
</tr>
</tbody>
</table>

### Table 8 – Strong and moderate/weak inducers and inhibitors of cytochrome P450 3A4 [69]

<table>
<thead>
<tr>
<th>CYP3A4 inhibitors</th>
<th>Moderate/weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir, indinavir, nelfinavir, erythromycin, telithromycin, clarithromycin, fluconazole, ketoconazole, itraconazole, nefazodone, grapefruit juice, verapamil</td>
<td>Cimetidine, buprenorphine</td>
</tr>
<tr>
<td>Phenyltoin, carbamazepine, oxcarbazepine, phenobarbital, efavirenz, nevirapine, modafinil, St. John’s wort, cyproterone, etravirine, rifampicin</td>
<td>Dexamethasone, felbamate, griseofulvin, pioglitazone primidone, troglitazone, rifabutin</td>
</tr>
</tbody>
</table>

CYP3A4 = cytochrome P450 3A4.
Delayed superficial wound healing 4 wk after surgery occurred in 20.9% versus 2% of patients in a matched historic cohort.

Similar experiences of neoadjuvant therapy with sunitinib [54] in 16 patients and sorafenib [55] in 30 patients showed an incidence of grade 1 complications according to the Clavien-Dindo classification [62] of 18.7% and 3.3%, respectively. While treatment with bevacizumab requires an off-therapy perioperative period of 8 wk, sunitinib [54] and sorafenib [55] could be safely administered up to 1 and 2 d before surgery, respectively, with a 3–4-wk postoperative interval before treatment reinitiation. For this reason, sunitinib and sorafenib appear more suitable than bevacizumab in the perioperative setting.

3.3.5. Patients with kidney failure

One attractive feature of currently available targeted agents is that their metabolism is mainly hepatic and is barely influenced by kidney failure, which can be expectedly common in a frequently nephrectomised population such as mRCC patients. Clinical experimental data for patients with severe kidney impairment, whether on dialysis or not, are scarce, as this subset of patient is generally excluded from clinical trials. In a retrospective report of 39 mRCC patients who presented with renal failure at baseline or developed it during therapy with sunitinib or sorafenib, renal insufficiency, defined as either a serum creatinine level of >1.9 mg/dl or a creatinine clearance of < 60 ml/min per 1.73 m², did not appear to be associated with unexpected toxicities.

This study also included two patients on dialysis: one treated with sunitinib, the other treated with sorafenib. Both of these patients tolerated treatment well and stopped it because of cancer progression [63]. Two case studies reported good tolerance of sorafenib used at full doses [64] and of bevacizumab [65], respectively, used at 50% reduced doses in two mRCC patients on dialysis. These data, along with a pharmacokinetic profile of targeted agents, suggest that targeted agents in mRCC patients with severe kidney failure, regardless of whether they are on dialysis, should be cautiously titrated to full doses, if possible, with close monitoring of renal function and toxicity as well as subsequent dose adjustments.

4. Conclusions

The unique sensitivity of kidney cancer to biologic therapy has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time. The variety of effective biologic agents has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time. The unique sensitivity of kidney cancer to biologic therapy has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time. The variety of effective biologic agents has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time. The unique sensitivity of kidney cancer to biologic therapy has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time. The variety of effective biologic agents has allowed a series of several therapeutic agents to be successfully tested and approved in a remarkably short period of time.

side-effects, dose reductions, and interruption of the anticancer medication. The management of toxic effects caused by targeted agents is of utmost complexity, so consultation with other medical specialists should always be encouraged, especially in the case of preexisting comorbidities and the onset of severe toxicity.

Author contributions: Giuseppe Di Lorenzo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Di Lorenzo, Buonerba.

Acquisition of data: Di Lorenzo, Buonerba.

Analysis and interpretation of data: Di Lorenzo, Porta, Bellmunt, Sternberg, Kirkali, Staehler, Joniau, Montorsi, Buonerba.

Drafting of the manuscript: Di Lorenzo, Buonerba.

Critical revision of the manuscript for important intellectual content: Di Lorenzo, Porta, Bellmunt, Sternberg, Kirkali, Staehler, Joniau, Montorsi, Buonerba.

Statistical analysis: Di Lorenzo, Porta, Bellmunt, Sternberg, Kirkali, Staehler, Joniau, Montorsi, Buonerba.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Di Lorenzo.

Other (specify): None.

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References


