The introduction of novel targeted therapies into the clinic in recent years has had a considerable impact on the management of several neoplastic diseases – such as gastrointestinal stromal tumors, hepatocellular carcinomas and renal cell carcinomas – considered until recently refractory to systemic therapies. We describe here two such novel biological agents, sunitinib and sorafenib, as a paradigm of the successful clinical application of new concepts. Sunitinib and sorafenib are small molecule tyrosine kinase inhibitors that target vascular endothelial growth factor receptor, platelet-derived growth factor receptor, C-Kit and others. Both agents are administered orally; sunitinib is typically given in cycles for 4 consecutive weeks with 2 weeks off, while sorafenib is given continually. Side effects occur in most patients, similar for both agents; they may affect several systems and organs but are mostly mild and easily manageable, rarely requiring discontinuation of the drug. However, these toxicities mandate prompt attention and intervention. The most frequently observed effects are hypertension, nausea, anorexia, asthenia and cutaneous manifestations; cardiac abnormalities may include congestive failure. Sunitinib, and markedly less frequently sorafenib, may cause thyroid gland dysfunction, mainly hypothyroidism. Antitumor activity has been shown for renal cell carcinoma in pivotal trials, for sunitinib as first-line treatment and for sorafenib in previously treated patients as second-line. Sunitinib is now approved as second-line therapy for patients with GIST refractory to imatinib; sorafenib has resulted in a significant prolongation in median survival in patients with hepatocellular carcinoma. Ongoing clinical trials will further define the spectrum of these agents’ antitumor activity, their role in combination with other drugs, as well as their optimal dose and schedule of administration.

Sunitinib (Sutent®, Pfizer Inc, USA) is a multitargeted tyrosine kinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, the stem cell factor receptor C-Kit, and others. Its main mechanism of action is through inhibition of tumor angiogenesis although it also has antiproliferative and apoptotic effects on diverse tumor types [1]. Sunitinib is metabolized by the cytochrome P450 3A4 system; strong inhibitors of this system such as cimetidine, erythromycin, ketoconazole and others, may increase plasma concentration of the drug, while CYP 3A4 inducers (such as barbiturates and corticosteroids) may decrease its plasmatic levels [2].

Typically, sunitinib is given at a dose of 50 mg once daily for 4 consecutive weeks followed by a 2 week rest. The dose does not need to be adjusted for age, weight, gender or performance status; however, pharmacokinetic data in patients with severe impairment of renal or hepatic functions are still lacking.

Sunitinib may result in a number of side effects that require close monitoring and, frequently, dose adjustments, temporary interruption, and sometimes even discontinuation of the drug. Patients must be informed about the potential side effects; they should learn how to identify them and should be encouraged to report them in real time to the treating physician. One should be aware that side effects of multitargeted drugs have a distinct pattern of toxicities that indeed differ from that traditionally observed with cytotoxic chemotherapeutic agents. The incidence of serious grade 3–4 toxicities is generally low, but they require prompt intervention.

The range of potential adverse effects is wide and may affect many systems and organs including gastrointestinal, cardiovas-
Sunitinib and sorafenib represent an example of a new class of anticancer agents, namely, multitargeted oral small molecule tyrosine kinase inhibitors, resulting in inhibition of tumor angiogenesis

Table 1. Sunitinib: incidence of frequent side effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>All grades</th>
<th>Grades 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Thyroid function tests abnormalities</td>
<td>85%</td>
<td>2%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>33%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
<td>8%</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>30%</td>
<td>–</td>
</tr>
<tr>
<td>Hand and foot syndrome</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>70%</td>
<td>6%</td>
</tr>
<tr>
<td>Bleeding (epistaxis)</td>
<td>18%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Table 1. Sunitinib: incidence of frequent side effects

Sunitinib may cause left ventricular dysfunction in about 10% of patients, and is clinically symptomatic in 1–2%. Baseline and periodic determination of left ventricular ejection fraction is necessary during treatment with sunitinib, particularly in patients with known cardiac risk factors. In patients with a decrease in left ventricular ejection fraction of ≤ 20% from baseline or below 50%, sunitinib should be temporarily interrupted; if overt congestive heart failure develops sunitinib should be discontinued [5]. Other potential cardiac events that are rarely observed include bradycardia and QT prolongation; therefore, the concomitant administration of sunitinib with QT prolonging agents such as halopendol, quinolone and macrolide antibiotics, and anti-emetics such as ondansetron and granisetron should be avoided.

Close monitoring of thyroid function is mandatory for patients receiving sunitinib. Thyroid function test abnormalities have been described in up to 85% of patients with renal cell carcinoma undergoing treatment with sunitinib. These abnormalities may occur very early, within 1–2 weeks from the onset of treatment with sunitinib, mostly hypothyroidism with elevated thyroid-stimulating hormone and decreased triiodothyronine and more rarely thyroxine, resulting in complaints such as fatigue, anorexia, fluid retention and intolerance to cold. Thyroid hormone replacement should be instituted promptly in these patients [6]. Rarely, thyrototoxicosis may precede hypothyroidism but burnout occurs rapidly and once hypothyroidism develops it may be profound. In patients on sunitinib, monitoring of thyroid-stimulating hormone should start at baseline and continue every 2–3 months during therapy as the incidence of hypothyroidism increases with more prolonged use of sunitinib. Sunitinib appears to cause follicular cell apoptosis with subsequent thyroiditis [6].

Sunitinib may cause a variety of dermatologic toxicities that develop typically 3 to 4 weeks from the start of treatment. These include yellow skin discoloration, observed in up to one-third of the patients, which is reversible upon discontinuation of the drug; hair depigmentation may occur as well, with normally pigmented hair regrowing during the off-treatment period. Yellow discoloration of the skin is due to the color of sunitinib and its metabolites, and hair depigmentation is caused by inhibition of melanocyte function through blockade of C-Kit signaling [7].

Painful hand and foot syndrome with erythema, edema and blisters on the palms and soles and occasionally with numbness and dysesthesia may occur frequently after 3 to 4 weeks from the start of sunitinib, requiring the use of moisturizers, skin care products, avoidance of pressure on affected areas, etc. [8]. Generalized skin rashes do occur rarely and are usually mild. Subungual splinter hemorrhages may also be observed and oral changes such as dry mouth and stomatitis, usually mild, may occur.

Gastrointestinal side effects include anorexia in 10–30% of the patients, nausea and vomiting (mostly moderate) and severe in less than 5% of the patients, and diarrhea in about 50% of the patients on sunitinib, being severe in about 5% of cases. In severe cases, sunitinib is discontinued until the diarrhea resolves and then resumed at a lower dose [9].

Profound myelosuppression from sunitinib, through inhibition of C-Kit, is uncommon, with grades 3–4 neutropenia and/or thrombocytopenia reported in less than 10% of patients, with blood counts usually returning to normal.
promptly. Blood counts should be obtained at the start of each new cycle; for recurrent grades 3–4 toxicity dose reduction of sunitinib is warranted. Mild bleeding, most commonly epistaxis, has been reported in up to one-fifth of patients on treatment with sunitinib; severe life-threatening bleeding is exceedingly rare [9].

Several laboratory abnormalities have been reported in patients taking sunitinib, including elevated lipase and amylase levels, without overt pancreatitis. Other laboratory abnormalities have included changes in glycemia, calcium, phosphorus and potassium, all of which can be readily corrected [10].

Clinical antitumor activity of sunitinib was initially demonstrated for renal cell carcinoma. The pivotal phase III clinical trial reported initially by Motzer et al. in 2007 [11] compared sunitinib with interferon-alpha as first-line therapy in 750 patients with metastatic clear cell renal cell carcinoma. The response rate was 37% for sunitinib and 9% for interferon, and the median progression free survival was 11 months and 5 months respectively for sunitinib and interferon ($P < 0.001$), establishing the former as standard first-line treatment for patients with metastatic renal cell carcinoma. In a recent update of their work [12], an overall survival advantage for sunitinib was also demonstrated (26.4 months median survival as compared to 21.8 months with interferon, $P = 0.05$). For patients who did not receive further therapies, the difference in median survival was more robust, 28 months for sunitinib vs. 14 months for interferon ($P = 0.0033$) [12].

In an international expanded access study of sunitinib in metastatic renal cell carcinoma, 4185 patients representing a heterogeneous population were included; some had been previously treated and a few had a low performance status; nevertheless, the median progression-free survival reached 11 months and the median survival was 19.8 months [13].

Maintaining adequate plasmatic levels of sunitinib seems to be important. A meta-analysis of three trials (two phase II and one phase III) in renal cell carcinoma showed that higher exposure to sunitinib was associated with an increased probability of response and a longer time to progression and survival [14]. It is in this regard that the administration of sunitinib using a continuous daily schedule at a dose of 37.5 mg is being investigated.

Ongoing studies with sunitinib in renal cell carcinoma include its administration in combination with other targeted therapies. Such a strategy is based on the simultaneous blockade of several signal transduction pathways. The administration of sunitinib and bevacizumab (Avastin®, Roche, Switzerland) is being investigated since the activity and safety of this combination has not yet been fully established.

The use of sunitinib as second-line therapy in renal cell carcinoma is also being pursued. In a recently published trial sunitinib was given following progression of the disease with sorafenib; an 18% partial response rate was achieved, and in 55% of the patients the disease stabilized. No correlation was found between response to sorafenib and subsequent benefit with sunitinib, suggesting limited cross-resistance between both agents [15]. Furthermore, the potential impact of sunitinib in the adjuvant setting following resection of the primary kidney tumor is being investigated in several clinical studies, including the STRAC trial (Sunitinib Treatment of Renal Adjuvant Cancer) assessing one year of sunitinib compared to placebo in high risk localized renal cell carcinoma after nephrectomy [16]. The three-arm designed ASSURE trial (Adjuvant Sunitinib and Sorafenib in Unfavorable Renal Cell Carcinoma) compares sunitinib vs. sorafenib vs. placebo following nephrectomy [16]. An EORTC trial is presently investigating the use of sunitinib before (neoadjuvant) or after (adjuvant) nephrectomy [16].

In addition to renal cell carcinoma, sunitinib is active against gastrointestinal stromal tumors. In a phase III clinical trial, 312 patients with GIST who had been treated with imatinib (Glivec®, Novartis, Switzerland) were randomized to receive either sunitinib or placebo. The median time to progression was 27 weeks with sunitinib and 6 weeks in the placebo arm ($P < 0.0001$), with a median overall survival advantage for the sunitinib-treated group (74 vs. 36 weeks, $P < 0.001$) [17]. A worldwide study in patients with GIST who were ineligible for a clinical trial or where clinical trials were not available included 1117 patients who were treated with sunitinib; their median time to progression was 41 weeks and the median survival reached 75 weeks. Prognostic factors affecting outcome included age, performance status and prior dose of imatinib [18]. Due to the potential risk for disease progression during the 2 week break of sunitinib administration, a trial of sunitinib given daily at a dose of 37.5 mg is ongoing in patients with GIST who progressed on imatinib. Of note, current data indicate that median survival times on treatment with sunitinib in patients with GIST are longer for C-Kit exon 9 mutations or wild-type c-kit/PDGFRA as compared to C-Kit exon 11 mutations, contrary to experience with imatinib where best responses are observed in patients with C-Kit exon 11 tumor mutations [19]. The concomitant administration of sunitinib and imatinib is now under investigation in patients with GIST whose disease progressed after imatinib alone.

Sunitinib and sorafenib are active in entities unresponsive to cytotoxic chemotherapy such as renal cell and hepatocellular carcinomas and gastrointestinal stromal tumors

PDGFR = platelet-derived growth factor receptor
SORAFENIB

Sorafenib (Nexavar®, Bayer Pharmaceuticals, USA) is a novel oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, C-Kit and the RAF-1 protein. It induces both tumor apoptosis and disruption of the tumor vasculature.

Metabolism of sorafenib occurs primarily in the liver by the CYP 3A4 system and by glucuronidation mediated by UGTIA9. The concomitant use of CYP 3A4 inducers may result in reduced plasma levels of sorafenib, but its metabolism is apparently not influenced by CYP 3A4 inhibitors. The co-administration of sorafenib with cytotoxic drugs that are conjugated by UGTIA1, such as irinotecan, docetaxel and doxorubicin, can result in increased levels of these agents [20]. Sorafenib is given at a dose of 400 mg twice daily, without dose adjustments for age, gender, weight or renal function. The dose of sorafenib for patients with pronounced liver dysfunction has not yet been established.

Side effects from sorafenib are similar to some, but not all, of those described in the previous section for sunitinib, and include fatigue, diarrhea, nausea, hand and foot syndrome, alopecia, bleeding and arterial hypertension.

Thyroid dysfunction is much less common than observed with sunitinib. Evaluation of thyroid function was carried out in 39 patients with renal cell carcinoma receiving sorafenib. While 21% had abnormalities in thyroid function tests, only 5% developed clinical manifestations of hypothyroidism [21]. Temporary dose reduction to 400 mg/day or the same dose every 2 days and/or discontinuation may be necessary for the management of side effects.

Sorafenib exerts antitumor activity in renal cell carcinoma as well. A phase III TARGET clinical trial by Escudier et al. [22] compared sorafenib with placebo in previously treated metastatic clear cell carcinoma of the kidney. The median progression-free survival was significantly longer in the sorafenib-treated patients, 24 weeks vs. 12 weeks in the placebo arm ($P < 0.001$); when an interim analysis was undertaken, 80% of the patients in the sorafenib group remained progression-free. These results led to Food and Drug Administration approval of sorafenib as second-line treatment in metastatic renal cell carcinoma.

Results of the TARGET trial were recently updated; overall survival analysis censoring the placebo patients demonstrated a survival advantage for sorafenib: 17.8 vs. 14.3 months, respectively [23].

Ongoing studies with sorafenib include its use as first-line therapy in renal cell carcinoma, alone compared to interferon, or in combination with the latter. Progression-free survival was similar for sorafenib and interferon as single agents at 6 months, but the sorafenib-treated patients had higher rates of tumor shrinkage and better quality of life scores. Clinical benefit was observed among patients in whom the dose of sorafenib was increased to 600 mg twice a day or with sorafenib crossover following progression of the disease on interferon [24]. The concomitant use of sorafenib and sunitinib in renal cell carcinoma is currently under investigation.

Sorafenib has been given in combination with bevacizumab in patients with renal cell carcinoma; while the response rate was substantial, 46% of 48 patients, increased toxicity was observed, mainly hand-foot syndrome and hypertension [25].

Sorafenib has also shown antitumor activity in collecting duct carcinoma, a rare variant of renal cell carcinoma [26], and in papillary and chromophobe renal cell carcinoma [27]. The use of sorafenib in the adjuvant setting in renal cell carcinoma is being investigated in the ASSURE trial (Adjuvant Sorafenib and Sunitinib in Unfavorable Renal Cell Carcinoma) [16]. The SORCE trial is comparing 1 or 3 years of adjuvant sorafenib compared to placebo following surgery in patients with primary renal cell carcinoma with intermediate or high risk for relapse [16].

Sorafenib is active in hepatocellular carcinoma, typically a chemoresistant disease entity. In a landmark phase III multicenter clinical trial, 602 patients with advanced hepatocellular carcinoma previously unexposed to systemic therapy were randomized to either placebo or sorafenib. Patients in the sorafenib arm experienced a significantly longer median survival, 10.7 vs. 7.9 months ($P < 0.001$) and median time to radiologic progression (5.5 vs. 2.8 months, $P < 0.0012$), when compared to placebo, a gain of about 3 months, notwithstanding a low objective remission rate of only 2% [28]. It should be emphasized that antitumor response rates to single-agent biologicals are consistently low when applying traditional Response Evaluation Criteria in Solid Tumors (RECIST), with a scarcity of complete remissions. The degree of tumor necrosis as evaluated by imaging studies rather than changes in overall tumor size seems to correlate better with patient outcome, prompting the adoption of novel, more appropriate endpoints to evaluate response to these agents. The Choi criteria, for instance, define a partial response as a decrease in tumor size of only 10% (or more), but with a decrease in tumor density of > 15% on computed tomography [29]. In patients with GIST following progression of the disease after both imatinib and
sunitinib, sorafenib resulted in a median survival of 13 months with 62% of the patients being alive at 1 year [30].

**CONCLUDING REMARKS**

In summary, the recent ongoing development of targeted therapies is having a substantial impact on the management of several malignant diseases. These agents have resulted in major achievements that influence the clinical course and prognosis of entities that until now were traditionally considered unresponsive to cytotoxic therapies, including renal cell carcinoma, hepatocellular carcinomas and GIST. Further directions include investigations on the optimal use of these newer agents in sequence or in combination, and on their place in the adjuvant and neoadjuvant settings.

Sequential administration enables maintaining a continuum of treatment with agents each given at full dose, targeting different pathways at different times. Sunitinib and sorafenib serve as a paradigm of the clinical impact achieved with a new generation of agents recently incorporated in to the anticancer armamentarium. Some targeted therapies are scheduled to continue for prolonged periods; the prompt and early detection of side effects is of utmost importance to reduce patient discomfort and to avoid dose reductions and/or interruptions of treatment.

**References**