Targeted therapies have dramatically improved the management of advanced renal-cell carcinoma (RCC) and gastrointestinal stromal tumours (GIST). Since 2006, three targeted therapies have been approved for RCC: sunitinib, sorafenib, and temsirolimus. First-line therapy with sunitinib improves overall survival compared with historical treatment of metastatic RCC, prolonging survival beyond two years. GIST, a rare and difficult-to-treat cancer, has had a poor prognosis historically. The introduction of targeted therapies improved one-year survival from 30% in the pre-targeted-therapy era to 90% with current agents. Imatinib, approved for GIST in 2003, is recommended as first-line therapy; sunitinib is now recommended for second-line therapy of GIST refractory to or progressing on imatinib. Speakers at a satellite symposium and at poster sessions discussed role of sunitinib in the management of advanced RCC and GIST.

Improved survival in metastatic colorectal cancer with first-line sunitinib

First-line therapy with sunitinib achieved more than two years overall survival in patients with metastatic RCC and was superior to standard therapy with interferon-α (IFN-α), according to final survival results of a Phase III study presented at ESMO at a poster session by Sylvie Negrier of the Department of Medical Oncology, Centre Leon Berard Lyon, France [1]. “Sunitinib remains a reference standard of care for the first-line treatment of patients with metastatic RCC,” Prof. Negrier stated.

The study enrolled 375 patients randomised to sunitinib and 360 randomised to IFN-α. Median overall survival in the sunitinib group was 26.4 months versus 21.8 months for IFN-α, which was marginally significant (p = 0.051). Prof. Negrier and colleagues suggested that the real survival benefit with sunitinib may have been greater. The survival end point could have been confounded by the 117 (33%) of patients assigned to the IFN-α arm who crossed over to sunitinib and by other anti-cancer drugs that patients took after the trial was ended. An exploratory analysis of patients who received study treatment only showed that median overall survival with sunitinib was twice that of IFN-α: 28.1 months versus 14.1 months, respectively (p = 0.003; Figure 1).

Cost-effectiveness of sunitinib
Three different posters presented at ESMO showed that sunitinib is cost-effective as first-line therapy for metastatic RCC according to economic modelling in Sweden [2], Spain [3], and the United States [4].

The economic model predicted superior outcomes with sunitinib compared to sorafenib, bevacizumab plus IFN-α, and temsirolimus for life years, progression-free life years, and quality-adjusted life years (QALYs). Moreover, sunitinib was found to be cost-saving compared with these agents.

The Markov cost-effectiveness model used in the three studies had a 10-year time horizon and simulated disease progression and survival and cost outcomes in a hypothetical cohort of adult patients with histologically confirmed metastatic RCC.
Patients were assumed to be treated until confirmed disease progression, at which point they were switched to second-line treatment or best supportive care. The model considered dose reductions, overall dose intensity, grade 3 and 4 treatment-related adverse events, and laboratory abnormalities.

In the Swedish study, using a threshold of SEK 500,000 QALY for societal willingness to pay for first-line treatment of metastatic RCC, sunitinib had the highest probability of being the most cost-effective therapy [1]. In the Spanish study, using the threshold of 30,000 Euros QALY, sunitinib had the highest probability of being the most cost-effective therapy of the other evaluated treatments [2]. Results were similar for the U.S. study with a threshold of $50,000–100,000 US QALY [3].

The first author of the Swedish study, Ulrika Hardenberg (Karolinska Institute, Stockholm, Sweden), said that the cost-effectiveness data combined with the new survival data showing extended survival beyond two years with sunitinib “support the role of sunitinib as the reference standard of care in metastatic RCC and predict its cost effectiveness versus other treatments” (Figure 2).

Figure 2  COST-EFFECTIVENESS RESULTS: 10-YEAR TIME HORIZON

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib vs</th>
<th>Bevacizumab + IFN-α</th>
<th>Temsirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental progression-free life years</td>
<td>0.49</td>
<td>0.21</td>
<td>0.36</td>
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<tr>
<td>Incremental life-years</td>
<td>0.33</td>
<td>0.07</td>
<td>0.02</td>
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<td>Incremental QALYs</td>
<td>0.27</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Incremental costs (SEK)</td>
<td>58,764</td>
<td>-420,647</td>
<td>-382,883</td>
</tr>
<tr>
<td>Incremental cost per progression-free (SEK)</td>
<td>120,270</td>
<td>Cost saving</td>
<td>Cost saving</td>
</tr>
<tr>
<td>Incremental cost per life-years gained</td>
<td>177,853</td>
<td>Cost saving</td>
<td>Cost saving</td>
</tr>
<tr>
<td>Incremental cost per QALY gained (SEK)</td>
<td>215,415</td>
<td>Cost saving</td>
<td>Cost saving</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-years; SEK = Swedish kroner


Optimizing treatment compliance with targeted therapy

Targeted therapies have changed the landscape of metastatic RCC management, but patients need comprehensive education and monitoring, and to be maintained on an optimal dose of drug as long as possible. Control of adverse events is required, explained Alan Ravaud (Department of Medical Oncology, Hôpital Saint André, CHU Bordeaux, Bordeaux, France).

The improvement in survival in metastatic RCC with targeted therapy comes with side effects. Commonly reported adverse events with sunitinib include fatigue, diarrhea, nausea, and stomatitis [5]. Sunitinib, sorafenib, and bevacizumab are associated with arterial hypertension; sunitinib, and to a lesser extent, sorafenib and bevacizumab are associated with asthenia; and both sunitinib and sorafenib are associated with hand/foot syndrome, Prof. Ravaud said.

Many patients have increased arterial blood pressure on anti-angiogenic therapy, and pre-treatment hypertension can delay initiation of treatment with targeted therapy. Treatment-induced hypertension occurs during the first three days of treatment, and can return upon re-initiation of treatment after it has been stopped. Blood pressure should be stabilised to about 130/80 mm Hg prior to treatment, and anti-hypertensive drugs should be used if necessary. During treatment, blood pressure should be monitored daily or at least three times a week. Treatment should be stopped if blood pressure reaches 170/100 mm Hg, Prof. Ravaud said.

Asthenia can be caused by several factors, including disease-related factors (the cancer itself and/or its treatment) and patient-related factors (such as age, nutritional status, and sleep disturbance). The hand/foot syndrome that occurs with anti-angiogenic therapy is characterised by paresthesias and burning pain on the palms and soles and is distinct from the hand/foot syndrome seen with chemotherapy. It occurs during the first three to four weeks of the first cycle of anti-angiogenic therapy and may resolve if grade 1 or 2, Prof. Ravaud noted.

Other potential side effects of targeted therapy include oral changes and mucositis, which usually resolves after one week of therapy, and hypothyroidism, which is seen more commonly with sunitinib than with sorafenib, he said.

Fatigue may be associated with treatment-induced hypothyroidism in patients taking sunitinib [4]. In a study of 73 patients treated with sunitinib, 66 had thyroid function tests available; of these 56 (85%) had one or more thyroid function abnormality consistent with hypothyroidism. Nine of 17 patients treated with thyroid hormone replacement showed symptomatic improvement. Patients on sunitinib should be monitored for hypothyroidism, and “consider hypothyroidism for patients taking sorafenib,” Prof. Ravaud said.

Dosing considerations

Targeted agents are cytostatic rather than cytotoxic, so maintaining adequate drug levels is key to controlling disease. Sunitinib can be used in two different regimens; the standard regimen is 50 mg/day for four weeks on and two weeks off (4/2) and continuous dosing at 37.5 mg/day is also an option. “You can give this drug both ways. There are no major differences in time to progression and overall survival between these two regimens,” Prof. Ravaud told the audience. “The 50 mg dose of sunitinib gives a better chance of tumour response, however, and it is important to start with the right dose.” Higher doses of sorafenib, 12 to 16 mg/day, are also preferable, according to a dose-escalated Phase II study of 44 patients with metastatic RCC, he added [2]. Another study showed that the highest exposure to sunitinib was associated with longer time to progression and overall survival in patients with metastatic RCC [7].
Although treatment with sunitinib therapy should be initiated at the optimal dose, adjustments in dosing may be required to manage side effects. To maximise use of targeted therapies at the optimal dose, patients should be educated about what to expect and be motivated. The risk-to-benefit ratio should be assessed, taking the patients’ risk factors into account. Comorbidities and risk factors should be stabilised prior to treatment initiation. Intensive support should be given during the first two cycles of treatment. Prompt effective management of side effects may require collaboration with the patient’s general physician.

Quality of Life

Although sunitinib is associated with side effects, as discussed by Prof. Ravaud, sunitinib treatment showed a consistent association with a lower symptom burden and improved health-related quality of life (HR-QoL) compared with standard IFN-α treatment in an international randomised Phase III trial [9]. Results of the study were presented at a poster session at ESMO by D. Cella (Center on Outcomes Research and Education, Evanston, IL, USA).

A total of 750 patients were randomised 1:1 to oral sunitinib 50 mg/day four weeks on and two weeks off or standard treatment with subcutaneous IFN-α. Forty-six per cent of the patients were recruited in the U.S. and 37% in the European Union. At the time of the analysis, patients had received up to 22 cycles of treatment. Mean age of patients was about 60 years.

In the total population, all HR-QoL end points were statistically superior in the sunitinib group compared with IFN-α. In the U.S. sub-population, all end point scores were significantly better in the sunitinib group, with the exception of EQ-5D scores. In the subpopulation from the European Union, differences in favour of sunitinib were seen for six out of nine EQ-5D scores. In the subpopulation from the European Union, significantly better in the sunitinib group, with the exception of IFN-α. In the total population, all HR-QoL end points were statistically superior in the sunitinib group compared with standard IFN-α treatment in an international randomised Phase III trial [9].

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In a randomised study of 946 patients with metastatic GIST, high-dose imatinib (800 mg/day) significantly improved progression-free survival from 21 months with standard-dose imatinib (400 mg/day) to 26 months (p = 0.026), median overall survival was five years [11]. However, toxicities were increased with the higher dose, Prof. Blay said. Another Phase III open-label trial comparing the two doses of imatinib in 746 patients with unresectable or metastatic GIST found no significant advantage to higher-dose imatinib [12].

Sunitinib is approved in Europe as second-line therapy for imatinib-resistant or imatinib-intolerant GIST. A randomised, double-blind, placebo-controlled, phase III study of 361 patients with imatinib-refractory GIST treated with placebo or sunitinib 50 mg/day in six-week cycles (four weeks on, two weeks off) showed significantly longer median overall survival with sunitinib: mean of 73.9 weeks versus 35.7 weeks.

New paradigms in GIST management

Imatinib is the treatment of choice for first-line therapy for unresectable GIST expressing stem-cell factor receptor (KIT) and/or metastatic GIST. Most patients treated with standard-dose imatinib (400 mg/day) will eventually develop resistance, which has been attributed to secondary mutations in the KIT gene [10]. Choice of second-line therapy for patients who progress on standard-dose imatinib should be based on consideration of primary resistance genotype, mutational status, and treatment tolerability, explained Jean-Yves Blay (Léon Bérard Comprehensive Cancer Centre, Lyon, France).

Before the availability of imatinib and sunitinib, median progression-free survival for patients with GIST was 1.5 months, and median overall survival was less than 12 months. With first-line imatinib therapy, the majority of patients with metastatic GIST will achieve tumour control, but about 12% to 14% will develop primary resistance and about 4% will be intolerant to imatinib, Prof. Blay explained. “In these cases, sunitinib is recommended,” he told listeners.

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<table>
<thead>
<tr>
<th>Symptoms and HRQoL endpoints</th>
<th>Total population</th>
<th>EU subpopulation</th>
<th>US subpopulation</th>
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<tr>
<td></td>
<td>SU</td>
<td>INF-α</td>
<td>Diff.</td>
<td>p value</td>
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<tr>
<td>FKSI (total score)</td>
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<td>41.51</td>
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<td>21.68</td>
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<tr>
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<td>74.05</td>
<td>66.23</td>
<td>7.82</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

*Significant p values
SU = sunitinib; INF-α = interferon-α; Diff. = sunitinib vs INF-α; FKSI = Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index; FKSI-DRS = FKSI Disease-related Symptom Subscale; EQ-5D Index = Euro-Quality of Life health utility index; EQ-VAS = EQ Visual Analogue Scale

Importance of mutations

KIT and PDGFR-α mutations play an important role in the development of resistance to targeted therapy and can influence outcome in GIST, Prof. Blay continued. KIT exon 9 mutations affect response to imatinib and progression-free survival. A larger number of mutations are sensitive to sunitinib compared with imatinib, he said.

“Proper treatment of GIST with imatinib depends on the presence of KIT exon 9 mutations, and this may also be true for sunitinib,” he said. He noted that exon 11 mutations have been observed in a small cohort of patients. Prof. Blay recommended mutational testing for all patients to optimise treatment choices in advanced GIST.

References


According to ESMO Consensus Guidelines, updated in 2008 in Annals of Oncology, first-line treatment of GIST is imatinib 400 mg/day and 800 mg/day if exon 9 mutations are present. “GIST tumours with KIT exon 11 mutations generally are sensitive to standard-dose imatinib,” he said, “while tumours with KIT exon 9 mutations may respond to imatinib 800 mg/day.” Recommended second-line therapy after imatinib 400 mg/day is imatinib 800 mg/day. Sunitinib should be used as second-line therapy for patients resistant to imatinib or who progress on imatinib. Tumours with wild-type genotype, KIT exon 9 mutations, or secondary KIT mutations in exon 13 or 14 may respond to sunitinib, according to a recent study [16], Prof. Blay commented.

Adjuvant use of imatinib is under study, and may turn out to be a worthy strategy to pursue. The ongoing ACOSOG 9001 trial is looking at randomisation to imatinib or placebo following surgery, and results of this trial will be forthcoming [16].

Prof. Blay noted that the current ESMO treatment algorithm may change depending on results of this adjuvant trial. Optimal sequencing of therapy with sunitinib versus imatinib 800 mg/day after progression on imatinib 400 mg/day is another area under study in GIST.