The role of surgery in EPP remains controversial. Less invasive methods are available for diagnosis and symptom control. Comparative survival benefits have been recorded from chemotherapy regimes alone.
Mesothelioma surgery can be complex and of high risk and should therefore be concentrated in specialized centres. There remiains a problem with equity of access to specialist skills, however. Well designed clinical trials are the best solution to these problems and the future aspiration of surgical enthusiasts.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
What are the side-effects of therapy in mRCC and how to handle them?

254 INVITED

Tyrosine kinase inhibitors

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The tyrosine kinase inhibitors have a range of side-effects which are only now becoming familiar to oncologists. Many of the toxicities are understated in their severity by use of the CTC. These criteria were developed for use with intermittent chemotherapy and it has become apparent that even grade 2 toxicities may significantly impair the quality of a patient's life. Often toxicities reported in studies are only really noticed if they are grade 3 or worse.
The main toxicities of TKI therapy are fatigue, rash, diarrhoea, hypertension, stomatitis, hypothyroidism and of particular importance in the neo-adjuvant or adjuvant setting, a potential to reduce healing. In addition there are emerging toxicities such as cardiac toxicity, the exact incidence and severity of which is still a matter for debate. Whilst most multi-targeted tyrosine kinase inhibitors exhibit most of the side-effects noted above, each tyrosine kinase inhibitor has its particular profile. For example, stomatitis and fatigue tend to be more marked with sunitinib. Rash tends to be more marked with sorafenib. Liver function disturbances tend to be more marked with pazopanib. Most of the side effects can be handled by patients, such that the large majority of patients are able to stay on treatment. Particular interventions may be useful to minimise the effect of side-effects and these interventions are often best used early in the course of a side-effect's natural history or even as preventative measures. The measures include using children's toothpaste and children's toothbrushes for stomatitis. Avoiding strong spirits or curries also for stomatitis. Diarrhoea may be handled by standard techniques such as loperamide. Hypertension should be rigorously controlled as evidence is accumulating that this reduces the risk of other cardiac toxicities. Standard agents may be used although care should be taken in choosing concomitant medications to use with tyrosine kinase inhibitors. Rash and hand/foot syndrome are often best managed preventatively by keeping the skin moist and supple with the use of emollient creams and occasionally urea-containing creams particularly where there is hyperkeratosis.
These side-effects, their severity and management will be discussed in the session. Mention will also be made of the possible future benefits of more precisely targeted tyrosine kinase inhibitors.

255 INVITED

mTOR inhibitors, bevacizumab

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Therapy of metastatic RCC has changed a lot in the past 3 years with approval of many new targeted agents. Due to the number of approved agents, and to the fact that very few patients (if any) are cured with these agents, side effects have to be taken into account both in terms of helping to choose the best drug to provide in each individual patient and in terms of management. In addition, toxicity should be considered differently when given chronically, since grade 1−2 toxicity is dramatically different when occurring for a few days or permanently.
Among targeted agents used in mRCC, mTOR inhibitors (temsirolimus and everolimus) and bevacizumab are very selective targeted agents, for which side effects are directly linked to the mechanism of efficacy, which might be different from tyrosine kinase inhibitors.

1. mTOR inhibitors mainly produce fatigue, skin rash and stomatitis. However, some less common side effects such as pneumonitis and algodystrophia should be known. Interestingly, most of these side effects are rapidly reversible when the drug is stopped. Metabolic dysregulation is directly due to mTOR inhibition. Usually mild, hyperglycemia, hyperlipemia might require adequate measures
2. bevacizumab has been used in oncology for more than 6 years and toxicity profile is well characterizes. VEGF inhibition induces hypertension, glomerular damages which can induce proteinuria and increased risk of bleeding and thrombosis. In RCC in addition, bevacizumab is given with interferon (IFN), and classical toxicity of IFN might be slightly increased by the addition of bevacizumab. However, specific side effects of bevacizumab appear similar to those observed without IFN, in other tumor types

In conclusion, a better knowledge of the side effects of the available drugs in RCC should help the physician to determine whether the benefit of a drug is large enough to justify its use in an individual patient.

256 INVITED

Do combination and sequential therapies have increased side-effects?

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Since 2005 the panorama of metastatic renal cell carcinoma (mRCC) treatment has radically changed, with four molecularly targeted agents (Sorafenib, Sunitinib, Temsirolimus and Bevacizumab – the latter in combination with Interferon) currently registered and available in European Union Countries, and two more (Everolimus and Pazopanib) presently under evaluation. Despite these dramatic improvements, no individual agent will benefit all mRCC patients, who should still be regarded as incurable; it is therefore mandatory to design rational clinical trials to try to further improve the results obtained so far. Two treatment strategies can be followed: to combine these agents, or to sequence them. Both strategies leave some questions open (do the mechanisms of action matter? does the target matter? in sequencing treatments, does the agent sequence matter? in combining treatments, is a 'horizontal' or a 'vertical' blockade better? and many more), but the issue of the tolerability of combination and sequential therapies appears to be key. Currently, available data are scarce and somehow biased. As for sequential treatments, we can mainly rely on retrospective series, while data relative to the safety of combinations come mainly from phase I trials, even though some of these combinations have already entered phase III development! Sequential therapies appear feasible, with a predictable and manageable adverse events profile and no signs of increased toxicity (except, probably, for fatigue and hypertension). Differently, combination treatments, while possibly providing increased activity, appear to be poorly tolerated, especially at full doses, and to cause even completely new toxicities (e.g. microangiopathic hemolytic anemia for the Sunitinib plus Bevacizumab combination). Furthermore, the choice of the agents to combine and the design of phase I studies proved to be extremely relevant when toxicity profile is taken into account. While waiting for the results of several phase II and III trials currently underway, we can say that the safety profile of combination treatments is somehow worrying (though there are some exceptions), while there is less concern for the safety of sequential treatments. To clarify not only activity but also safety issues, specific and well designed studies are badly needed.

257 INVITED

Cytokines and vaccines

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In mRCC the standard of care in Europe has, until the recent introduction of the targeted agents, been interferon alpha 2a (IFNα-only) based on the results of several randomised trials. In particular, the MRC RE01 study which showed a modest but clinically and statistically significant overall survival advantage for IFNα over MPA.
Interleukin-2 (IL2) when given intravenously at high dose by bolus injection results in response rates of 14−23% (13−15) but more importantly, about 7% of patients obtain a durable complete remission lasting over three years and some of these have been maintained for ten years. However, no randomised trial has ever shown a survival advantage for this treatment over a control group.
The toxicity profile of immunotherapy with IFN and IL2 is related to the aspecific nature of the treatment. In the largest trial in RCC, randomising IFNα versus INF, interleukin 2 (IL2) plus fluorouracil (FU) (IIF) in patients with previously untreated mRCC, no differences in PFS and overall survival exist. The toxicity is however different: during treatment there was significantly more grade 3/4 toxicity associated with IIF compared to IFNα-only (56% versus 38%, $p < 0.001$). Fatigue was significantly worse for IIF patients with 22%, 45% 24% and 2% experiencing grade 1, 2, 3 and 4 fatigue respectively, compared to 34% 39% 17% and <1% in IFNα-only patients. There was no evidence of significant differences between treatment arms in terms of worst quality of life score for tiredness, lack of appetite, shivering or lack of energy. Serious adverse events were reported in 6% and 5% of patients receiving IFNα-only and IIF, respectively.