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Letter to the Editor

Reply: Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-α2a compared with sunitinib

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Sir,

We welcomed the response and debate regarding treatment-related costs in metastatic renal cell carcinoma (RCC) provided by Charbonneau (Pfizer, USA) and Sandin (Pfizer, Sweden) (Charbonneau and Sandin, 2010). However, there are several points in their letter we would like to address.

Novel therapies for the treatment of metastatic RCC have different tolerability profiles, which are largely based on differences in mechanism of action (Schmidinger and Zielinski, 2009). Side effects of therapy may have a different impact on individual patients, with the potential to disrupt well-being, daily activities/function and overall quality of life. The management of side effects is a concern for physicians due to the potential for temporary or permanent withdrawal of therapy to manage side effects, meaning that patients may receive a suboptimal treatment benefit. The management of side effects also represents additional costs for payers and contributes to the total cost of therapy.

Two of the standard first-line treatment options for patients with metastatic RCC, bevacizumab + IFN and sunitinib, have largely different safety profiles. Vascular endothelial growth factor (VEGF)-related side effects such as hypertension are observed with both therapies, but non-VEGF-related side effects such as hand-foot syndrome are also seen in patients treated with sunitinib (Escudier *et al*, 2007; Motzer *et al*, 2007). Our original paper outlined that bevacizumab + IFN is associated with lower adverse event management costs than sunitinib, largely based on the difference in tolerability profiles. These data are supported by another recent analysis of healthcare costs in the United States that reported that the adverse event management costs for bevacizumab are 2 – 3 times lower than those for sunitinib (Oh *et al*, 2010).

One point that we would like to reiterate is that there is strong evidence to indicate that bevacizumab + IFN has similar efficacy to sunitinib in patients with metastatic RCC. The two pivotal trials for these therapies in metastatic RCC showed that both bevacizumab + IFN and sunitinib significantly improved progression-free survival (PFS) compared with IFN, with a median PFS of 10.2 and 11.0 months, respectively. Furthermore, a robust meta-analysis performed by the Cochrane Collaboration concluded that bevacizumab + IFN provides similar efficacy to sunitinib in untreated patients with metastatic RCC (Coppin *et al*, 2008).

In our original publication, we addressed the papers by Thompson-Coon *et al* and Mills *et al*, both of which suggested that sunitinib is significantly more efficacious than bevacizumab + IFN (Mills *et al*, 2009; Thompson Coon *et al*, 2009). A significant limitation of these analyses is the inclusion of data for bevacizumab + IFN from CALGB 90206, an open-label phase III trial with some important differences in patient demographics compared with AVOREN. We argue that a valid indirect comparison of PFS should only use the pivotal trial data, performed under the same conditions and providing the same quality of data (independent radiology review of PFS from controlled, blinded studies that are not comparable to open-label studies). Furthermore, a recent analysis of independently assessed PFS data from AVOREN and the phase III sunitinib trials reported that there is no significant difference in first-line PFS between sunitinib and bevacizumab + IFN (HR = 0.94 (95% CI: 0.69 – 1.29; $P = 0.709$)) (Mickisch *et al*, 2010a, b). Additionally, repeating the Mills *et al*, analysis, which is more conservative than the Thompson Coon analysis, with the investigator assessing data from the pivotal trials of sunitinib and bevacizumab + IFN results in a non-significant PFS HR of 0.83 (95% CI: 0.64 – 1.06; $P = 0.13$) (Mickisch *et al*, 2009a, b).

It is well recognised that non-VEGF-related side effects such as fatigue, GI events, HFSR, myelosuppression, diarrhoea, mucositis and rash, although often not severe, can have an impact on the patient's quality of life (Porta and Szczylik, 2009). Therefore, an ability to effectively manage side effects and get patients and/or carers back to work may represent a hidden cost benefit that has not been addressed in cost-related analyses to date and should help to reduce health-related costs.

As we outlined in our paper, adverse event management costs vary for each country and for each side effect. For example, haematological adverse events, which are reported more frequently with sunitinib than with bevacizumab, are likely to have the highest management costs and therefore a greater impact on the total adverse event management costs. Another consideration is that some adverse events may be experienced for prolonged periods and may require repeated treatment measures, which may not be captured by an analysis such as ours.

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Charbonneau and Sandin stated that our analysis may have overestimated the costs associated with the management of some adverse events, based on a lower cost for the treatment of grade 3/4 thrombocytopenia reported in the latest UK National Health Service costs (2010). This observation is correct as we used an older version of the UK National Health Service costs (NHS reference costs 2006–2007), based on the timing for development and submission of our original paper. However, the reported incidence of grade 3/4 thrombocytopenia with sunitinib is higher than that seen with bevacizumab + IFN and therefore the proportional cost for this side effect will remain higher for patients treated with sunitinib.

Overall, treatment-related costs are likely to include acquisition costs, administration costs and costs related to the management of adverse events. Drug acquisition costs will evidently vary due to country-specific initiatives agreed between the healthcare authorities and pharmaceutical companies. In consequence, overall treatment costs are not a primary consideration if looking at cross-country trends and differences as a scientific objective. In contrast, secondary costs such as costs associated with the treatment of adverse events are directly related to the drug involved and largely independent of the pricing strategies of the manufacturer. We agree that the management of adverse event costs is comparatively small compared with that of acquisition costs. However, adverse events and their management may substantially impact on patient quality of life, remain independent of the acquisition costs and hinder physician care. This is most important from a clinician's point of view.

Taking into account all healthcare-related costs, including any differences in drug acquisition costs and costs related to the management of adverse events, an analysis of healthcare costs based on the Italian healthcare system reported comparable annual costs for bevacizumab + IFN and sunitinib (Ravasio, 2009). Moreover, an analysis based on healthcare costs in the United Kingdom by the National Institute of Clinical Excellence (NICE) reported that bevacizumab + IFN and sunitinib had comparable incremental cost-effectiveness ratios: £53 820 and £50 000, respectively (NICE, 2009).

The management of adverse events has important implications for patients, physicians and payers. In the absence of direct head-to-head clinical assessment, a model such as ours is currently the only available way to assess the costs associated with the management of adverse events, which may help to facilitate the decision-making process.

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