Hypertension as a predictive factor of Sunitinib activity

Sunitinib malate is a new reference standard for the treatment of metastatic renal cell carcinoma (mRCC) [1, 2]. Clinical or biological markers of activity and toxicity are warranted due to large variations in treatment response, as well as side effects. Hypertension is a major toxicity observed after most antiangiogenic treatments and is a potential signal of drug exposure. We aimed to retrospectively analyze a putative correlation between sunitinib activity and hypertension.

Forty patients (32 men) treated in a compassionate program with sunitinib after cytokines failures for mRCC were enrolled between October 2005 and August 2006, for a 6 month follow-up period. Patients received sunitinib given orally at a starting dose of 50 mg per day in repeated 6-week cycles (4 consecutive weeks followed by 2 weeks off treatment). Adverse events were graded according to NCI CTC criteria.

The Median age was 58 years (range 39–78). All the patients had at least 2 cycles of treatment and 10 patients had controlled arterial hypertension. Assessment of response determined by RECIST criteria [3] showed 14 partial responses (PRs) resulting in an overall response rate of 35%, 20 patients (50%) with stable, and 6 patients with progressive disease (15%). The median progression-free survival has not yet been reached (31 patients remained alive at 9 months follow-up). The most common clinical grade 3 (no grade 4) adverse events were: dysgeusia (27.5%), fatigue (25%), and hypertension (22.5%), which are consistent with the known safety profiles of sunitinib [1].

The pattern of toxicity was compared among responders (PRs) and non-responders (stable or progressive disease). In univariate analysis using the 2-tailed Fisher exact test, a higher response rate was observed in patients with stomatitis (P = 0.015), fatigue (P = 0.019), hypertension (P = 0.02), testicular erythema (0.04), as well as hair depigmentation (P = 0.042). The number of metastatic site >1 (P = 1), initial performance status >0 (P = 0.50), high serum calcium level (>100 mg/L) (P = 0.38), high lactate dehydrogenase level (P = 0.22), and low hemoglobin level (P = 0.73), were not statistically associated with response. In multivariate analysis using logistic regression, appearance or worsening hypertension (grade 2 or more) was found to be the single independent predictor of a better clinical response ([β = 0.85, SD = 0.32], OR, 2.33, (95% CI, 1.69–3.22); P = 0.009). Furthermore grade 3 hypertension (requirement of therapy or more intensive therapy than previously) was correlated with a better outcome ([β = 1.74, SD = 0.81], OR = 5.69 (95% CI, 2.51–12), P = 0.03 (Table 1).

The appearance of hypertension, particularly grade 3, was associated with higher treatment response to sunitinib in mRCC. Early and intensive antihypertensive therapy with the goal of maintaining the sunitinib use may improve response rate in those patients. Discontinuation of treatment because of hypertension should be revised. The clinical value of this association remains to be established in future larger studies including prospective pharmacodynamics/pharmacokinetics analysis.

O. Rixe1, B. Billemont1 & H. Izzedine2*

1Departments of Medical Oncology and 2Departments of Nephrology, Pitie-Salpetriere Hospital, Paris, France

(*Email: hassan.izzedine@psl.aphp.fr)

Table 1. Relationship between hypertension and objective response to sunitinib

<table>
<thead>
<tr>
<th>Hypertension no (%)</th>
<th>Patients (n = 40)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Nonresponders</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (42.9)</td>
<td>3 (11.6)</td>
</tr>
<tr>
<td>Grade &lt;3</td>
<td>8 (57.1)</td>
<td>23 (88.4)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>

References

doi:10.1093/annonc/mdm184

© 2007 European Society for Medical Oncology