Interleukin-2 continuous infusion and angiogenesis surrogate markers in metastatic renal cell carcinoma

Recently many advances have been pursued in the biology and clinical development of vascular endothelial growth factor (VEGF)-target therapy in renal cell carcinoma (RCC). However, any complete response (CR) has yet to be demonstrated, moreover the durability of the eventual responses is still under evaluation [1, 2]. Therefore high dose Interleukin-2 (IL-2) therapy remains the therapeutic approach that provides the highest rates of durable CR [3]. Unfortunately, response rates are still very low and clearly new therapeutic approaches are needed for the treatment of metastatic RCC. The combination of immunotherapy with IL-2 and anti-angiogenesis drugs appears to be one of the best options under investigation.

It is well-known that during IL-2 administration a complex activation of the cytokine network is ongoing, but few data are available about the effect of this activation on angiogenesis. Up to now, the most studied surrogate markers of angiogenesis are: VEGF metalloproteinase-2 (MMP2) and MMP9; in RCC it has been established that VEGF and MMP-2 and MMP9 are over-expressed in RCC tissues and the expression does correlate with the stage of the disease [4]. Moreover, there is some evidence that high levels of VEGF in serum can be associated with tumor progression [5].

We believe that in order to optimize the design of the schedule of combination treatment with IL-2 and anti-angiogenetic drugs the effect of Il-2 on angiogenesis and its surrogate’s markers are needed.

In our Institution, patients with metastatic RCC undergo two cycles of the following schedule of IL-2 intravenous continuous infusion (iCI): IL-2 10 Million International Unit (MIU) iCI 5/7 days, one week off followed by IL-2 10 MIU iCI 5/7 days followed by other 4 weeks off.

We evaluated the effect of this therapy on the activation of angiogenesis measuring the plasma level of VEGF, total MMP2 and MMP9 with commercial ELISA Test (R&D Systems Europe Abingdon UK) before, during, and after the 5 days iCI, in 13 patients with metastatic RCC: eight males, five females, median age 56 years (range 43–59).

In the 13 patients analyzed we found the following mean level of plasma VEGF (773 ± 378 pg/ml) MMP2 (55.9 ± 19.9 ng/ml) and MMP9 (1146 ± 498 ng/ml). The baseline mean values of VEGF MMP-9 showed a trend to correlate with the number of metastasis.

We did not observe any significant increase of VEGF, MMP2 AND MMP9 during the 3 days of IL-2 infusion as well as after 24 hours from the end of the 5-day iCI. On the contrary, at the same time-points we observed the activation of pro-inflammatory cytokine network measured by the significant increased levels of neopterin Interferon-γ, tumor necrosis factor-α, and soluble Icam (before IL-2 versus 3-day iCI $P < 0.001$, $P = 0.004$, $P = 0.004$ and $P < 0.001$, respectively;
before IL-2 versus 24 from the end 5-day iCI \( P = 0.0002, \)
\( P = 0.002, \) \( P = 0.004, \) \( P < 0.001, \) respectively).

This preliminary observation demonstrates that IL-2 iCI does not affect the release of angiogenic surrogate markers such as VEGF MMP2 and MMP9, even if it highly activates the release of pro-inflammatory factors. On the basis of our data, we can suggest that the most suitable time-to-test angiogenesis inhibitors during IL-2 therapy, appears to be the interval between IL-2 administrations and not concomitantly when the most severe side effects are expected and no significant increased releases of angiogenic factors have been observed.

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