circulating interleukin-6 as a tumor marker for hepatocellular carcinoma

I have read with great interest the paper by Porta et al. [1] on circulating interleukin (IL)-6 as a promising tumor marker for hepatocellular carcinoma (HCC).

I have appreciated the attempt of the authors to put the 'pleiotropic' cytokine IL-6 not only in the context of its complex biologic activities but also to attribute it to a clinically meaningful role as a more sensitive marker in identifying HCC than serum alpha 1-fetoprotein.

I agree with the authors who found that IL-6 values were highest in patients with advanced disease: indeed, we have studied in several of our papers the serum levels of IL-6 in different populations of cancer patients and found that they were correlated with advanced disease, i.e. tumor stage (III–IV), performance status, nutritional status and in particular they were highest in patients with cancer-related anorexia cachexia [2–4]. Moreover, in the multivariate regression analysis, IL-6 resulted as the main independent factor predictive of clinical outcome, i.e. survival, in advanced cancer patients, especially when cachectic.

The above findings have been confirmed by Porta’s paper who found (Table 3) that IL-6 titers were significantly higher in patients with more advanced disease (Cancer of the Liver Italian Program: CLIP score >3 versus CLIP scores 1–3).

Notwithstanding the numerous probatory findings by Porta supporting at least a certain degree of ‘specificity’ in favor of IL-6 as a tumor marker for HCC, I am still doubtful as to whether IL-6 may be considered a significant marker of ‘advanced’ neoplastic disease rather than a specific marker of HCC. A somewhat supporting evidence for this might come from IL-6 values in cirrhotics (25th–75th percentile: 2.6–10) which slightly overlap with those of HCC-CLIP scores 1–3 (25th–75th percentile: 9.24–28.6 and much more as for range values).

It is clear that the main clinical interest of Porta’s paper is to have demonstrated the ‘diagnostic value of IL-6 assessment which is significantly increased when it is associated with a dosage of alpha 1-fetoprotein’.

Additionally, I would also comment on Porta’s finding under ‘Results’ section (page 355) that ‘10 patients who were treated with high dose MAP for a month had highly reduced IL-6 titers’ and the statement under 'Discussion' section (page 357) that ‘We also demonstrated that IL-6 production can be efficiently down-regulated in vivo by giving our HCC patients the progestational anabolizing agent MAP, which confirms previous findings in other tumors in both the preclinical and clinical settings’. In several of our papers, since 1995 [5], we have repeatedly demonstrated that synthetic progestagens, both MAP and megestrol acetate, are able to down-regulate IL-6 levels in vivo in cancer patients but, more importantly, in one specific paper [6], we have directly demonstrated that MAP, added in vitro into culture of cancer patients peripheral blood mononuclear cells (PBMCs) at a concentration very similar to that reached in the serum of cancer patients therapeutically treated with MAP (500–1000 mg day), was able to reduce the IL-6 production and release by the same PBMCs, thus directly explaining the mechanism of action by which MAP provides clinical benefit in cancer patients with high IL-6 serum titers.

My final comment is to welcome all the research addressed to exploit the role and clinical significance of IL-6 in neoplastic diseases.

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references


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