Temsriolimus in metastatic renal cell carcinoma

Metastatic renal cell carcinoma was considered for decades a hopeless cancer, with only limited treatment options. The recent development of what is generally referred to as ‘targeted molecules’ opened new treatment options and substantially improved the prognosis of patients suffering from this disease. The carcinogenesis of the main histologic subtype of renal tumours, the clear cell type, is dominated by the vascular endothelial growth factor (VEGF) dependence of tumour cell growth [1]. Indeed, the mutation or impairment of the VEGF gene that is commonly observed in these tumours induces an accumulation of a transduction factor called hypoxia-inducible factor (HIF), which is a key element for the adaptation of cells to hypoxic conditions. The accumulation of HIF in renal tumour cells favours the expression of a number of downstream genes involved in cell proliferation, neoangiogenesis, etc. The renal tumour cell itself produces large amounts of VEGF, as well as overexpressed VEGF receptors, thus creating an autocrine loop in which VEGF is a major tumour growth factor [2]. It also induces, as expected, the development of a dense neoangiogenesis phenomenon. The very first demonstration of a clinical efficacy of an anti-VEGF treatment in patients with metastatic renal cell carcinoma was made in 2003 [3].

The interest of bevacizumab, an anti-VEGF antibody, was recently confirmed by the results of a randomised phase III trial [4]. Meanwhile, two other anti-tyrosine kinase molecules targeted to block the VEGF receptor, i.e. sorafenib and sunitinib, have been shown to be effective for the treatment of these patients, as also demonstrated by randomised phase III trials [5, 6]. In this issue, Bellmunt et al. [7] report on the safety profile and toxic effects of temsirolimus in advanced renal cell carcinoma patients with poor prognostic features. This is actually the fourth molecule which has proven activity in this disease. Contrary to previously tested agents, temsirolimus does not exert a direct anti-angiogenic activity. It is an inhibitor of the mTOR kinase which is a key element in the regulation of the cellular metabolism. The mTOR kinase is a major element of the cell signalling pathway which causes the cell to grow and proliferate and has also been shown to regulate apoptotic cell death. The mechanism of action of temsirolimus on angiogenesis and on the VEGF dependence of renal cell cancer tumour cells is probably not so straightforward. However, the known interactions between the mTOR kinase and HIF, as well as PDGF, another well-known tumour growth factor for renal cancer, can explain its activity [8]. In addition, interactions with the PTEN gene, which is often altered in a minor histologic subtype of renal cancer, the papillary type, are probably more or less involved in the activity of the compound [8]. For these reasons, it seems reasonable to hypothesise that this agent will finally find a role complementary to that of more direct anti-angiogenic agents in the treatment of renal cancer. The effects of temsirolimus on renal cell carcinoma were detected early during the phase I trial of the drug, then confirmed by two phase II trials [9–11]. The efficacy of the drug was conclusively proved by the results of a large randomised phase III trial comparing temsirolimus versus interferon-α versus the combination of both drugs in patients with poor prognosis features [12]. The report by Bellmunt et al. [7] provides a focus view of adverse events observed in patients receiving temsirolimus, as part of this randomised trial published by Hudes et al. [12] in 2007. In this report, patients receiving temsirolimus had a 3.6-month survival advantage over patients receiving interferon-α. One must keep in mind that the trial was conducted on a subset of high-risk patients and that the overall survival of patients treated with temsirolimus did not exceed 1 year. Therefore, it is important to put in the balance the side-effects of the drug which is now marketed in European countries. Bellmunt et al. [7] state, in the conclusion of their summary, that "Temsirolimus related adverse events […] in general did not negatively impact patient quality of life". This assumption is based only on the opinion of the authors since no quality of life results are provided, either in this report or in the main previously published report [12]. The second statement in this conclusion is that "Temsirolimus-related grade 3–4 adverse events were primarily metabolic in nature and easily controlled medically". Metabolic abnormalities (hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, hypophosphatemia and hypocalcaemia) actually represent an important part of the grade 3–4 adverse events observed on temsirolimus. A limited number of these abnormalities require specific treatment. However, it is also true, even if not calculated by the authors, that if these events are excluded, temsirolimus-related grade 3–4 toxic effects still represent 54% of all-grade events. Therefore, we advise the readers to be cautious with the conclusions of this report which has been written at the initiative of Wyeth Pharmaceuticals to accompany the recent marketing of their product in Europe. On the other hand, the readers will gain interesting information on temsirolimus-induced toxic effects as well as on the different ways to overcome or limit them, since the risk-benefit ratio remains a major issue for this subgroup of patients with poor outcome.
references