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Mini Review

New Neurological Disorders in a New Patient. Long Term VEGFR Inhibitors Effects

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Introduction

Currently, several cancer therapies are based on neutralizing anti-VEGF antibodies and small-molecular-weight tyrosine-kinase inhibitors that target the VEGFRs. These new strategies for cancer treatment show the clinical relevance of inhibiting VEGF signal-transduction pathways that are exaggerated in pathological angiogenesis.

Angiogenesis is mediated by the stabilization of the master transcription factor, leading to transcription of a number of cancerogenic factors. Vascular endothelial growth factors (VEGFs) are crucial regulators of vascular development during embryogenesis as well as angiogenesis in the adult. In mammals, five VEGF ligands have been identified. These ligands bind, in an overlapping pattern, to three receptor tyrosine kinases (RTKs), known as VEGF receptor -1, -2 and -3, as well as to co-receptors. Inhibiting VEGF activity by targeting the growth factor itself or its receptor is a strategy underlying a wave of targeted oncological therapies[1].

The first clinically available VEGF signaling pathway (VSP) inhibitor, bevacizumab, a monoclonal antibody targeted against soluble VEGF protein, was approved by the Food and Drug Administration in 2004 for the treatment of metastatic colon cancer[2].

These agents, who interrupt critical cell signaling pathways involved in cancer angiogenesis and growth, comprise three primary categories: monoclonal antibodies directed against specific proangiogenic growth factors and/or their receptors; small molecule tyrosine kinase inhibitors (TKIs) of multiple proangiogenic growth factor receptors; inhibitors of mTOR. Activation of VEGF receptor by VEGF induces expression of nitric oxide synthase in endothelial cells, which promotes vascular permeability and vasodilation. Accordingly when VEGF agonists were used in an attempt to promote angiogenesis in models of ischemic cardiomyopathy, hypotension was one of the major side effects. In patients being treated with VEGF inhibitors, several studies observed a loss of parallel capillary circulation in normal tissue[3].

Thus when using angiogenesis inhibitors in the long-term treatment of cancer it will be important to preserve pathways that are important for the survival of blood vessels in healthy tissues.

Neurological adverse events and side effects are common and class-specific in oncology during and after a treatment. Currently peripheral neurotoxicity's is well recognized as consequence of classic antiballistic therapy but the new drugs as antibodies and immunoactive medications implement nervous central system toxicity risk and draw a completely new and different scenario.

VEGFR Inhibitors: Side Effects

The overall toxicity associated with VEGFR inhibitors is low compared with other chemotherapy drugs, although they are commonly associated with skin and gastrointestinal adverse events[4].

Hypertension and Proteinuria

The most frequent and specific side effects of anti-angiogenic targeted therapies are hypertension and proteinuria. Clinical trials with bevacizumab identified hypertension in 28% of the patients; trials with sorafenib, sunitinib, and pazopanib identified hypertension with similar frequency[5].

For anti-angiogenic drugs overall, the incidence of hypertension varies according to the characteristics of patients (age, previous history of hypertension, comorbidities) and according to the characteristics of the drug prescribed (type of drug, dose, and schedule used): bevacizumab induces hypertension by a decrease in VEGF-induced nitric-oxide synthesis and by the rarefaction of capillary bed, while sorafenib induces hypertension by not clear mechanisms [6-7]. Nevertheless, an absolute blood pressure increase occurs in the majority of patients, with rapid onset after the first administration of the drug.

However, these data may underestimate the true incidence of hypertension in clinical practice today; patients in the general population may have more comorbidities or be at increased risk of developing VSP inhibitor–induced hypertension compared with highly selected trial patients. There is a paucity of data to guide management of VSP inhibitor–associated hypertension.

In this scenario only recently the classification system used by the National Cancer Institute to assess toxicities associated with novel chemotherapies has been updated to more closely reflect the Seventh Report of the Joint National Committee on Prevention,

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Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) guidelines. The committee made four recommendations: formal risk assessment for potential cardiovascular complications before initiation of treatment with VSP inhibitors; recognition and treatment of pre-existing HTN before initiation of VSP inhibitor therapy; active monitoring of blood pressure (BP) throughout treatment; and treating to a BP goal of less than 140/90 mm Hg (and 130/80 mm Hg in patients with chronic kidney disease or diabetes mellitus)[8].

Thrombo-Embolic Events and Bleeding

In a meta-analysis that assessed arterial thrombo-embolic events (one of the major causes of myocardial ischaemia and cardiac infarction), among 12,617 patients from 20 randomized controlled trials, was shown how patients receiving bevacizumab had a significantly increased risk of arterial thrombo-embolic events (RR 1.44; 95% CI 1.08–1.91), with an incidence of thrombo-embolic events of 3.3% (2.0–5.6%)[9]. This toxicity was also seen with sunitinib and sorafenib, which carried a relative risk for arterial thrombotic events of 3.03 compared with placebo[10].

Bevacizumab, was associated with a statistically significant increase in serious bleeding, even if severe bleeding is rare during treatment with antiangiogenic drugs.

Epistaxis, haemoptysis, haematemesis, gastrointestinal bleeding and stroke, have been described as severe and mortality-related adverse effects in patients treated with sorafenib. In a phase III trial in patients with renal cell carcinoma, the rate of bleeding was higher in the sorafenib arm (15%) than that of the control arm (8%), but severe bleeding were comparable (3% versus 2%, sorafenib versus control, respectively). In a meta-analysis of 27 trials with sunitinib and sorafenib, the overall bleeding rate was 16.7%, with 2.4% considered to be severe events[7].

Cardio Toxicity and Atrial Fibrillation

Original clinical trials of Angiogenesis inhibitors were not designed with standardized cardiac end points other than hypertension. For this reason, most reports of cardio toxicity other than hypertension come from observational studies. Since the approval of these agents, observational studies of sunitinib and sorafenib have demonstrated rates of symptomatic heart failure ranging from 3% to 8% and rates of decreased left ventricular ejection fraction of at least 15%, ranging from 8% to 28%. A decline in left ventricular ejection fraction (LVEF) and acute coronary syndrome can be caused by antigenic inhibitor administration.There is increased incidence of atrial fibrillation in patients treated with VSP inhibitors, although it is unclear whether this is due to hypertension[7].

Neurotoxicity and Neurological Adverse Events

The most common neurological adverse events are headaches, arterial cerebrovascular events, and posterior reversible leukoencephalopathy syndrome. Posterior reversible leukoencephalopathy syndrome should be considered in patients with acute neurological symptoms and high blood pressure, renal failure, or autoimmune disorders. The patho-mechanism is related to blood–brain-barrier disruption due to endothelial injury by abrupt blood pressure changes or inflammatory cytokines. Usually neurological adverse events occur as acute or chronic encephalopathy and with unspecific symptoms such as peripheral neuropathy, weakness, delirium, cognitive impairment (chemobrain), aphasia, paresis, apraxia, cerebellar disorders and hallucinations. Chronic encephalopathy from cancer therapy is typically seen after whole-brain irradiation and high-dose chemotherapy and the symptoms are indistinguishable from rapid progressive vascular changes, radiation-induced leukoencephalopathy or infectious. Cerebellar disorders have also been reported with several VEGFR drugs. The differential diagnosis of treatment-associated cerebellar syndromes includes paraneoplastic cerebellar degeneration, a paraneoplastic syndrome frequently associated with non-small-cell lung cancers[11].

Stroke

The importance of an acute ischemic neurological deficit is evident in the scenario of cancer management that is tied to the paraneoplastic coagulation disorder to the arterial hypertension or to the inflammation of larger vessels. The management according to international guidelines might include both systemic thrombolysis and also local intra-arterial thrombectomy. Moreover the antiblastic therapy should be halted or discontinued to avoid bleeding complications; indeed a severe neurological complication VEGF inhibitors is brain haemorrhage, which has been reported especially for patients with cancer and brain involvement[12].

Conclusion

The major advances in cancer management that occurred have resulted in improved survival and in disease chronicity[13]. Physicians should be aware of treatment associated neurotoxicity, but currently they are not able to recognize long term neurotoxicity treatment related; thus in the near future with the new scenario of cancer survivor, neurological sequelae or immune-related neurological adverse events induced by treatment of systemic cancer will be some of the most important challenges in patient survivorship. In our opinion we can certainly emphasize how angiogenesis inhibitors represent a new frontier in the target cancer therapy and in the personalized cancer care. However there are still too few data available about the side effects of these drugs that act by blocking physiological mechanisms as angiogenesis and their long-term effects. Thus in the near future, the scenario will be reshaped by new patients (long cancer survivors), with new symptoms and signs of neuro-vascular pathologies, which will be related to new drugs. These patients will be not, anymore oncologists patients but neurologists, geriatricians, cardiologists, should take care of them, specialists that have to reinvent their profession. How to manage this new condition? What are the long-term side effects?

There are many questions that we should ask about this new patient in the near future.

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