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Original Research

Acute neurovascular events in cancer patients receiving anti-vascular endothelial growth factor agents: Clinical experience in Paris University Hospitals

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Cerebral radiotherapy

Abstract ***Background:*** Despite the increasing and broadening use of agents targeting the vascular endothelial growth factor (VEGF) pathway, little is known on their acute neurovascular toxicities.
Methods: This retrospective, multi-centre study examined the characteristics of patients with solid tumours who experienced an ischaemic or haemorrhagic stroke, a transient ischaemic accident (TIA) or a posterior reversible encephalopathy syndrome (PRES) while under anti-VEGF and until 8 weeks after termination of treatment and evaluated their management in our institutions from 2004 to 2014. Patients with newly diagnosed or progressive cerebral metastases at the time of the acute neurovascular event were excluded.
Results: Thirty-four patients (55.9% men) were identified, and experienced either ischaemic stroke (n = 18), PRES (n = 9), TIA (n = 6) or haemorrhagic stroke (n = 1). At initiation of anti-VEGF agents, 64.7% of patients had previous cardiovascular risk factors, and 52.9% had hypertension. Eight patients (23.5%) had received cerebral radiotherapy, five of which concomitantly to anti-VEGF treatment. Six (17%) patients died in the 8 weeks following the acute neurovascular event, and only 55.9% recovered their initial neurological status. Overall, 1-year and 2-year survival rates after the acute neurovascular event were 67.9% and 50%, respectively. When anti-VEGF agents were reintroduced (n = 6), severe vascular toxicity recurred in two patients.
Conclusions: Neurovascular events under VEGF treatments are potentially severe, and the management of comorbid conditions has to be improved. A prospective collection of data and standardised management of such events is therefore being structured in our institutions.

1. Introduction

The use of anti-vascular endothelial growth factor (VEGF) agents has dramatically expanded during the past decade, either as single-agent or concomitantly to chemotherapy, for the treatment of various solid tumours [1,2].

Across indications, hypertension was identified as a class toxicity of anti-VEGF agents [3–6], raising concerns on their cardiovascular and neurovascular toxicities [7].

Regarding the latter, two recent meta-analyses on arterial thromboembolic events have pointed out a relative risk (RR) of ischaemic stroke of 1.37 and 3.22 and a RR of haemorrhagic stroke of 3.09 [3,8]. However, only few neurovascular events were reported in these two meta-analyses.

The clinical features, optimal management and impact on global prognosis of stroke occurring under anti-VEGF agents are poorly documented in the literature.

Recently, posterior reversible encephalopathy syndrome (PRES), a clinical entity often related to hypertensive encephalopathy [9], also appeared as a rare class toxicity of anti-VEGF agents [10,11].

Whether clinical characteristics of patients such as cardiovascular risk factors, the onset of hypertension while under anti-VEGF agents and cumulative doses received could identify a population at risk remains unknown.

Besides, the optimal management of acute neurovascular events in this patients' population remains to be defined, as well as their impact on disease prognosis.

Finally, whether anti-VEGF agents could be reintroduced after the occurrence of an acute neurovascular event is uncertain.

In this context, we designed a multicentre, retrospective study in Paris University Hospitals, in order to better describe clinicobiological and imaging features, modalities of current management and outcomes of patients with solid tumours treated with anti-VEGF who experienced acute neurovascular toxicities.

2. Patients and methods

2.1. Participants

We performed a retrospective medical record review of consecutive patients with solid tumours treated with anti-VEGF agents in our institutions from January 2004 to June 2014. Briefly, the heads of the departments of Medical Oncology and Neurology affiliated to the Universities of Paris for residency programs were contacted by phone or email. In addition to cases identified by electronical medical record search, additional cases were sought based on physician recall. Each medical record was reviewed manually, and if needed, imaging was reviewed with neuroradiologists from the above-mentioned institutions.