Hemorrhage caused by antiangiogenic therapy within previously irradiated areas: expected consequence of tumor shrinkage or a warning for antiangiogenic agents combined to radiotherapy?

In this issue, Hui et al. [1] report their experience from a phase II trial evaluating the use of sunitinib in recurrent nasopharyngeal carcinoma (NPC) previously treated with high-dose radiotherapy.

This trial has been prematurely halted after two patients died of epistaxis and/or hematemesis within the first 4 weeks of therapy. The limited number of patients, 14, recruited into the trial renders it certainly difficult to exploit the data in terms of antitumor efficacy. However, unexpected toxicity, when encountered during clinical trials, always questions retrospectively about the validity of the scientific rationale. Our capacity to a posteriori decipher and analyze the underlying physiopathology of unexpected side-effects should be developed in order to improve the safety of our clinical research and daily practice.

The evidence for vascular endothelial growth factor (VEGF) overexpression in NPC biopsies, the efficacy of antiangiogenic therapy in preclinical models of NPC makes no doubt regarding the justification to the use of antiangiogenic agents in such a poor prognosis situation. Thus, the question is twofold: where these toxic effects unavoidable or the consequence of the downsizing of locally advanced tumors eroding blood vessels? Or alternatively, do we have hints from existing preclinical and clinical data that the likelihood of hemorrhage could have been increased in this situation?

head and neck tumors a common cause of bleeding

Tumor hemorrhage and bleeding has been reported to frequently occur in series of advanced head and neck cancer patients [2]. Common causes of intractable hemorrhage associated with head and neck neoplasms are spontaneous tumor bleeding, rupture of pseudoaneurysms as a result of iatrogenic vessel injuries, intra-arterial infusion chemotherapy, and local tumor irradiation [3]. Repeat hemorrhage following radiation or chemotherapy is a common troubling complication in patients with advanced head and neck cancer.

Common side-effects of radiochemotherapy for head and neck tumors are erythema, erosion and ulceration of the skin and mucosa, xerostomia, interstitial lymphedema, fibrosis of the soft tissue, and, in severe cases, necrosis of bone or cartilage. Radiation-induced late effects like chronic inflammation, organ dysfunction, fibrosis, and necrosis are driven in part by vascular alterations. Vascular changes contain premature atherosclerosis with stenosis, adventitial fibrosis, and weakening of the arterial wall caused by obliteration of the vasa vasorum [4, 5]. However, acute rupture of irradiated large vessels is a rare but life-threatening complication [6]. Most of the vascular erosions of cervical arteries appear in patients with complications like recurrent tumors, wound infections, or pharyngocutaneous fistulas [7].

radiotherapy produces vascular damage to normal tissues

Several lines of evidence suggest that the parameters of radiotherapy, namely total dose and fractionation may affect the risk of hemorrhage. First, the consequences of radiotherapy on the vascular compartment are more pronounced when irradiation is carried out using high dose per fraction, >2 Gy/day fraction conventionally used [8]. Secondly, hemorrhage occurs more often in the setting of re-irradiation where the cumulated total radiation doses are high. In the current trial, most patients received previous high-dose radiotherapy or even radiochemotherapy regimens, not only considering the cumulated radiation dose delivered, which is often >70 Gy, but also considering the fractionation size (the daily radiation dose) since fractionation doses ranging from 2.5 to 8 Gy were used as a boost to the tumor. Converting these radiation doses delivered in their radiobiological equivalent of radiotherapy delivered in a conventional 2 Gy/day, five times a week, provides total equivalent cumulative doses way >80 Gy for late complications of radiotherapy.

The fact that a vast proportion of the patients experiencing bleeding in the current series received such an intense radiotherapy regimen might have increased the vascular mucosal damage. Of note, potential imbalance of the proportion of patients treated with high doses or altered fractionation radiotherapy regimens is not presented in the patient group who did not experience bleeding. Such information might have been useful to incriminate, at least partially, the role of radiotherapy fractionation and total dose in the generation of vascular damage.

antiangiogenic agents cause bleeding

In a meta-analysis assessing the risk of bleeding with sunitinib or sorafenib in cancer patients, Je et al. [9] carefully reviewed 23 studies, including four well-conducted randomized controlled
Initially, antiangiogenic therapies were expected to be active healing and the menstrual cycle. Several lines of evidence clearly suggest that late effects of radiation therapy involve a chronic wound healing reaction associated with permanent matrix remodeling normal tissues. Damage to the vascular compartment is also an important aspect of radiation late effects to normal tissues [17]. In addition, experimental findings suggest that irradiation of endothelial cells increase their sensibility to anti-VEGF therapies [18].

Bleeding complications, gastrointestinal perforations, and disturbed wound and ulcer healing can all occur as a result of antiangiogenesis therapy [19] and are most probably caused by disturbance of the tight endothelial cell–platelet interaction that maintains vascular integrity.

VEGF has a role in the coagulation cascade by inducing tissue factor (TF) expression on endothelial cells [20]. TF is the main regulator of the coagulation cascade, inducing thrombin formation from prothrombin, which in turn activates platelets and converts fibrinogen into fibrin to cause clot. The inhibition of angiogenesis might be partly mediated by the down-regulation of TF expression by endothelial cells. Endothelial cell-induced coagulation promotes wound healing and presumably angiogenesis. Therefore, inhibition of the TF pathway might be responsible for inadequate wound healing.

Altogether, these data suggest that angiogenesis is an important component of the normal tissue response after irradiation where angiogenesis inhibition might impact the wound healing reaction.

**pharmacological parameters might increase the bioavailability of sunitinib**

Tyrosine kinase inhibitors such as sunitinib are prescribed at a fixed dose, independent of body weight or body surface area. Whether the pharmacodynamics of these drugs is independent of these measures remains an open question. Importantly, because the daily oral doses of antiangiogenic tyrosine kinase inhibitors are fixed, toxicity patterns may be increased in patients with low body weight or sarcopenia features [21] and decreased in patients with high body weight. A relatively low body weight in this trial population might have contributed to a relative overdose of sunitinib. Beside the continuous administration scheme, a 2 weeks on/2 weeks off schema has been proposed for sunitinib in order to improve tolerance [22]. One hypothesis is that such an alternative schema might have allowed some time for normal tissue repair and a better tolerance in this trial.

**the combination of radiotherapy and systemic therapy can be challenging, notably in the era of molecular targeted agents**

Radiation recall is a relatively infrequent well-known side-effect of drugs when administered after radiotherapy that is usually moderate and spontaneously recovers. Radiation recall syndrome has been mostly reported after chemotherapy use (gemcitabine, liposomal doxorubicin). Interestingly, radiation recall is now being reported after targeted therapies (cetuximab,
bevacizumab, mammalian target of rapamycin inhibitors) [23–25].

On the opposite, the severe bleeding events observed in the current trial are far more challenging as they are of major concern. Treatment of cancer involves a widespread use of radiotherapy in conjunction with chemotherapy not only at the locoregional stage but also in the course of systemic metastatic disease. Both treatments are associated with well-known, nonoverlapping, profiles of tolerability. The recent increase in the use of targeted antiangiogenic therapies currently approved for metastatic cancers such for kidney, liver, and colon cancer will without doubt increase situations where radiation therapy will be administered during or even sequentially with antiangiogenic therapy. We believe that the recent severe bleeding events encountered in the present trial should be considered as a warning for clinicians. In particular, radiotherapy regimens are capable of inducing more late normal tissue damage than standard radiotherapy such as hypofractionated or single-fraction radiotherapy. These techniques are today routinely not only used for palliative irradiation but also tend to generalize in the setting of cranial and extra cranial stereotactic radiotherapy that are too often considered nontoxic. Novel high-tech radiotherapy tools will then have to be considered with caution when combined with novel drugs, even in the case of sequential use.

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disclosure

The authors declare no conflict of interest.

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