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Re: Irinotecan-Related Cholinergic Syndrome Induced by Coadministration of Oxaliplatin

Valencak et al. (1) have recently reported a case of cholinergic syndrome in a phase II study of oxaliplatin combined with CPT-11.

The patient presented the adverse event when CPT-11 was given 1 hour after oxaliplatin, while no side effects were observed when CPT-11 was given 1 day after oxaliplatin. This anecdotal episode with two positive rechallenges led the authors to suggest that there is a potential interaction between the two drugs.

The CPT-11/oxaliplatin combination has been explored in phase I studies in France, and preliminary results have demonstrated it to be a safe regimen and active in patients with 5-fluorouracil-resistant colorectal cancer. More than 50 patients have been treated with over 250 cycles of this therapy given every 2 or 3 weeks (2,3). We have not seen any evidence of enhanced incidence or severity of CPT-11-related toxicity. No pharmacokinetic interaction between the two agents has been detected (4). The only finding concerning increased toxicity was the observation of severe CPT-11-related toxicity (neutropenia and/or diarrhea) in two patients with Gilbert’s syndrome (5,6). With a strong pharmacologic rationale, we considered that this phenomenon was attributable to impaired metabolism of CPT-11’s active metabolite, SN-38, in patients with deficient hepatic glucuronidating activity.

Hyperacute cholinergic syndrome has been well described, although it is variable in its pharmacodynamics (rate of onset and severity); it has been attributed to the piperidine structure of the CPT-11 molecule, which mimics a cholinergic drug when liberated by esterases to form SN-38 (7).

No increase in the incidence or severity of cholinergic syndrome has been observed in the French trials. However, all patients in these trials received 0.25 mg of prophylactic atropine, given subcutaneously a few minutes before CPT-11, as is customary in many centers that routinely administer CPT-11 according to the European thrice-weekly schedule.

Although the preliminary recommended dose for the combination of CPT-11 and oxaliplatin is 60% of the single-agent recommended dose for either agent, so far we do not have evidence of enhanced cholinergic reaction with this combination.

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References


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Louis, Paris.
Re: Gene Therapy Strategies for Tumor Antiangiogenesis

In their interesting and thorough review of antiangiogenic gene therapy, Kong and Crystal (1) argue for targeting only tumor-associated vessels and not targeting normal angiogenesis. But in some settings, it also might be of value to target normal angiogenesis.

Gene therapy, the delivery of genes by gene carriers (i.e., transfer vectors) or antiangiogenesis therapy, the administration of antiangiogenic drugs themselves to solid tumors, may be hampered in tumors with low perfusion. We have worked with experimental tumors implanted into the livers of rats. These tumors, as human liver cancers, have a predominantly arterial vascular supply. Temporary hepatic arterial occlusion for 2 hours renders the main part of the experimental tumor necrotic without development of collaterals. However, tumor regrowth takes place in the periphery (2,3). Outside the peripheral necrosis of the tumor, granulation tissue with presumably normal capillaries appear, as around all types of necrosis. Cell division (i.e., mitosis) occurs in these capillaries and, of course, in vessels in the regrowing tumor. Therefore, it appears to be of value that, in this setting and in other settings with emerging granulation tissue around the tumor, the antiangiogenic genes and/or drugs are effective against host capillaries as well as against tumor vessels. We do not know if extraportal spread from the liver might be influenced by such treatment.

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References


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Response

In reference to the letter written to the Journal regarding our review article of antiangiogenic gene therapy, we agree that these strategies may also target angiogenesis in the local milieu of the tumor in addition to tumor-associated vessels. Although there are differences from normal in tumor-associated vessels in regard to structures, such as fenestrations, and in surface molecules, such as the αvβ3 integrins, most antiangiogenesis strategies do not distinguish tumor-associated vessels per se. This is one advantage of gene therapy over systemic antiangiogenesis therapy, in that the gene therapy is usually employed as a local therapeutic strategy, thus limiting toxicity in distant organs utilizing angiogenesis as part of the normal biology of the organs.

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Editor's note: R. G. Crystal has equity in, and is a consultant to, GenVec, Inc., a privately held biotechnology company located in Rockville, MD. GenVec is a development stage company engaged in the business of designing and manufacturing vectors (biologic materials that are used to transfer genes to humans to correct hereditary or acquired disorders therapeutically).

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Erratum: “Identification of Melanoma Antigens That Are Immunogenic in Humans and Expressed In Vivo,” by Applebaum et al. [J Natl Cancer Inst 1998;90:146–9 (Issue 2)]. On page 146, in the “Materials and Methods” section, under the heading “Melanoma Vaccine,” the procedure described for the preparation of the melanoma vaccine failed to mention that SF-HM54, one of the four cell lines used, was of xenogencic (hamster) origin. The other three lines were derived from allogeneic human melanoma cells. This correction does not change the results of the study since, in all cases, the antigens that were identified were expressed in vivo by human melanoma cells. The authors regret the error.