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LETTERS AND COMMENTS

Angiostasis-induced vascular normalization can improve photodynamic therapy

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In a recent issue, *Cellular and Molecular Life Sciences* published on the combination of photodynamic therapy (PDT) and anti-angiogenesis for the treatment of cancer [1]. In this paper, Bhuvaneswari and colleagues elegantly review this field. The idea behind combining these two therapeutic strategies is based on the observation that PDT can lead to vessel closure, and hence hypoxia, as well as other tissue damage resulting in inflammation. This combination of hypoxia and inflammation can in turn cause the enhanced release of angiogenic growth factors (vascular endothelial growth factor, VEGF) followed by the regrowth of the targeted neoplastic tissue. Thus, it appeared logical to try to block the VEGF pathways after PDT, for instance by applying antibodies against VEGF. This type of combination therapy is not limited to the treatment of cancer. Indeed, for the treatment of certain forms of exudative macular degeneration, recently published results from a phase II clinical study demonstrate great promise for the combination of PDT (Visudyne) together with anti-VEGF-A therapy using humanized antibody fragments (Lucentis). PDT as a monotherapy has clearly been shown to be effective in treating some early stage superficial cancers. However, for more advanced cancers, where PDT monotherapy appears to be less effective, the usefulness of the photodynamic approach followed by anti-VEGF therapy has not yet been extensively demonstrated in the clinic.

For the treatment of advanced cancer, there has been recently significant interest in the use of vascular normalization [2] by the application of anti-angiogenesis compounds like the above-mentioned anti-VEGFs. Such inhibitors of angiogenesis can, at least in part, reverse the situation of abnormal leaky and tortuous vasculature in the tumor to make a more normal vascular phenotype. This vascular normalization has been shown in tumor models to normalize both the interstitial perivascular pressure as well as the tissue oxygenation. The transient normalization of the abnormal structure and function of advanced tumor vasculature following the application of angiogenesis inhibitors was put forward as the explanation of the sometimes spectacular beneficial effects observed when applying angiostasis prior to chemotherapy or radiation therapy.

This induced angiogenesis inhibition leads to (1) temporarily normalized tissue pressure and therefore to the possibility of enhanced exposure and sensitivity of the tumor cells to chemotherapeutic compounds, and (2) enhanced tissue oxygenation, making the tumor cells more vulnerable to radiotherapy [2, 3]. It should be noted that this normalization has the potential to reduce the heterogeneous features, of the vasculature in particular, which characterize virtually all cancers. This is of importance because heterogeneity of cancer properties may underlie the failure of many current treatment regimens including anti-angiogenesis therapy itself. The efficacy of PDT for the destruction of tumor tissue is based on intravascular thrombotic events and/or a direct destruction of cells in the perivascular tumor tissue, both through mechanisms

Comment on Bhuvaneswari R, Gan YY, Soo KC, Olivo M (2009) The effect of photodynamic therapy on tumor angiogenesis. Cellular & Molecular Life Sciences, 66, 2275-2283.

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involving photochemical induction of toxic reactive oxygen species. Hence it is not unreasonable to expect that normalization of the oxygen pressure in the tumor tissue following anti-angiogenesis induced vascular normalization, should also lead to an increased and more homogenous effect of oxygen-dependent PDT. Consequently, it may be hypothesized that anti-angiogenesis treatment might be effectively scheduled not only after PDT but also in a carefully chosen time gap, possibly of a few days, before PDT [3]. The timing of the normalization window will probably depend on the mechanism of the angiogenesis inhibitor used. Of course, the carefully optimized combination of multiple anti-angiogenesis agents acting via different pathways may be even more efficient for this purpose than the single-agent approach as discussed above. The time-dependent biodistribution and mechanism of action of the photosensitizer are among the other important factors to be optimized in the combination therapy.

As is clear from the Bhuvaneswari paper, efforts to schedule the anti-angiogenesis treatment before PDT as a treatment of malignancies are very sparse, and essentially restricted to case reports. An example of such a case report, in which anti-angiogenesis is applied clinically prior to PDT, has been provided recently by Sagong et al. [4]. This paper discusses two patients with circumscribed choroidal hemangioma, who were treated with intravitreal injection of Avastin and subsequent PDT with Visudyne. The result of this clinical application on a very limited number of patients turned out to be very successful indeed, since complete regression of the lesions was observed in these patients for 6–9 months. Furthermore, the reported improved visual acuity was accompanied by complete resorption of subretinal fluid and macular edema.

If, however, following the normalization of the vasculature induced by the anti-VEGF therapy, the exposure to these compounds is excessively prolonged, this may lead to a reduction of the blood vessel density, and even less provision to the tumor of oxygen and therapeutics. Thus it is proposed here that PDT is to be applied in the time window where blood vessels are “normalized”, i.e., well before vessel number reduction, when the tissue oxygen levels are still relatively high.

Some reports have suggested that PDT following (or occurring simultaneously with) angiogenesis inhibition would be equally effective, or possibly less beneficial, than PDT prior to anti-angiogenic therapy [5]. However, these studies were not specifically designed with the goal of benefiting from vascular normalization, and the angiogenesis inhibitor may consequently have been applied outside the optimal time slot of vascular normalization and enhanced oxygenation.

Finally, it should be mentioned that the major current challenge for the improvement of PDT is the introduction of better targeting of photosensitizers in order to more selectively treat the diseased tissues. Still, the improvement of PDT efficacy through vascular normalization and the subsequent homogenization may also be very useful, in particular for the application of PDT to cases of advanced cancer. We favor the view that there is a window of opportunity for PDT following anti-angiogenesis vascular normalization. It should be understood that systemic treatment with angiogenesis inhibitors can have side-effects such as anti-thrombotic activity and hypertension [6]. It is to be envisioned that co-treatment for such indications is a valid option [7]. We would furthermore like to underline that the anti-angiogenesis modality in this combination therapy may well be applied in the form of a drug cocktail that interacts via multiple complementary pathways [8], and that the optimal combination treatment conditions may also depend on such parameters as the proliferation of the tumor blood vessels. It is for these reasons that we conclude here that more research is needed to systematically test the optimal relative timing in the combination of anti-angiogenesis therapy and PDT for the treatment of cancer.

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