Multiple Etiologies of Tumor Hypoxia Require Multifaceted Solutions

Commentary on Crokart et al., p. 630

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In this issue of Clinical Cancer Research, Crokart et al. (1) report that glucocorticoids increase tumor oxygenation by decreasing oxygen consumption rate. The magnitude of the improvement in $pO_2$ is sufficient to cause a 70% prolongation of tumor growth time when given before a single large dose of 25 Gy. This effect occurs despite the fact that this treatment decreases perfusion. The results of this paper highlight the complexity of oxygen transport deficiency in tumors, which is the subject of this commentary.

It has been recognized for well over half a century that hypoxic cells are more radioresistant than normoxic cells. Many clinical studies have shown that the prognosis for patients who have hypoxic tumors is consistently worse than for those who have well-oxygenated ones (2). Many methods have been tested to improve tumor oxygenation in attempts to improve radiation response; the majority have focused on improving oxygen delivery. Augmented delivery strategies tested in phase III trials have included hyperbaric oxygen (3), agents that right shift the hemoglobin saturation curve in combination with oxygen breathing (4), carbogen (95% oxygen + 5% carbon dioxide) + nicotinamide (a vasoactive vitamin B analogue) in a trial referred to as ARCON (accelerated radiotherapy with carbogen and nicotinamide), and erythropoietin (5, 6). Although the hyperbaric oxygen trials successfully improved local tumor control following radiotherapy, this modality is cumbersome and impractical for daily use with modern radiotherapy practice (3). Phase III trials of ARCON in invasive bladder (7) and head and neck cancer (6) are currently enrolling patients. A phase III trial radiotherapy + epoetin $\beta$ in head and neck cancer patients tested the hypothesis that the maintenance of hemoglobin concentration above a threshold would improve treatment outcome. Tumor oxygenation was not measured, but amelioration of tumor hypoxia via prevention/correction of anemia was implicit in the study design. Administration of erythropoietin in this study did in fact result in higher hemoglobin concentrations, but survival was unexpectedly worse in the experimental group (5). The value of using blood transfusions for anemic patients to improve radiotherapy outcome is also doubtful (8). Presently, there is no level 1 evidence supporting the value of any method of improving tumor oxygenation.

The oxygen concentration at any tissue location represents the net balance between delivery and consumption. A framework for understanding oxygen transport in tumors has been established using a combination of experimental data and theoretical models (9, 10). Factors that contribute to inefficiencies in delivery include irregularities in vascular orientation and a sparse (11) and vasoconstricted arteriolar blood supply (12). Vessels that are far removed from the arteriolar source can be relatively hypoxic, even when perfused (13). Relative vascular hypoxia can increase red cell rigidity, which increases blood viscosity and reduces red cell flux (14, 15).

Computer simulations have been done, based on experimentally derived data, comparing effects of increasing blood $pO_2$, or perfusion rate versus reduction in oxygen consumption rate to eliminate tumor hypoxia (10). The relative decrease in consumption rate needed to abolish hypoxia was less by a factor of 30 than the relative increase in $pO_2$ needed to produce the same effect (Fig. 1).

Many methods to improve oxygen delivery to tumors have been investigated preclinically; a few are discussed here as examples. Improving oxygen concentration of blood by breathing normobaric hyperoxic gases is relatively inefficient because hemoglobin is virtually 100% saturated in room air. Increasing oxygen concentration will only increase plasma oxygen concentration, which is not efficiently retained within the vasculature. In one tumor model, arteriolar oxygen concentration averaged around 20 mm Hg during air breathing; it doubled to 44 mm Hg during carbogen breathing (11). Blood gas measurements, in contrast, averaged 100 and 480 mm Hg, respectively. The decline in vascular $pO_2$ along the afferent path (longitudinal gradient) is typical of normal tissues (16, 17). Importantly, the longitudinal gradient is steeper when hyperoxic gases are used. The 5-fold increase in blood gas $pO_2$ only translates into a 2-fold increase in tumor arteriolar $pO_2$. This magnitude of change is insufficient to overcome hypoxia, as predicted by computer simulations (Fig. 1; ref. 10). Hyperbaric oxygen, however, has been reported to virtually eliminate hypoxia and improve radiotherapy response, whereas normobaric hyperoxic gas breathing alone was minimally effective compared with air breathing (18, 19). These results present a validation of the theoretical simulations discussed above which were based on the same tumor model.

Improving tumor perfusion is difficult because vasoactive drugs usually decrease tumor perfusion by creating vascular steal. The decreased driving pressure reduces perfusion in the face of greatly elevated flow resistance in tumors (20–24). Sonveaux et al. made a significant contribution by showing that inhibition of endothelin-1 receptors can significantly improve tumor perfusion, oxygenation, and radioresponse (12). Tumor arterioles were surprisingly found to be vasoconstricted under baseline conditions; blockade of endothelin-1 led to nitric oxide release, vasorelaxation, and increased perfusion.
Hypoxia and acidosis increase red cell rigidity and suspension viscosity by causing crenation (14). Elevated viscosity increases flow resistance. The calcium channel blocker, flunarizine, was shown to restore normal cell shape, normalize blood viscosity, and improve tumor microvascular oxygenation by facilitating higher blood flow rates and hematocrits, specifically in relatively hypoxic microvessels (14, 15). Calcium channel blockers have also been reported to increase radiation response as a result of improved oxygenation (25). Interestingly, the steroid, methylprednisolone, has also been reported to reduce red cell suspension viscosity (26). This effect may have partially ameliorated the effects of steroid-induced tumor hypoperfusion, as shown in this study.

In the current study (1), perfusion was monitored using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and a semiquantitative histologic method involving direct visualization of patent blue staining, following i.v. administration. A reduction in “perfused area” was observed. However, the relatively macroscopic methods used do not rule out the possibility that perfusion was redistributed at the microvascular level toward hypoxic microvessels. Additionally, the simulations shown in Fig. 1 illustrate that diminished oxygen consumption rates can improve oxygen transport through tissue 10 times more effectively than they would be reduced by a comparable relative decrease in perfusion. Thus, it is theoretically possible for tumor oxygenation to improve even in the face of diminished perfusion.

The preceding discussion illustrates the complex and multifactorial origins of tumor hypoxia. Accordingly, it seems logical to use combinations of treatments to improve tumor oxygenation. Surprisingly, few studies testing this concept, including methods to reduce oxygen consumption (27), have been reported. To our knowledge, such an approach has only been reported once. Hyperglycemia was used to reduce oxygen consumption rate by inducing the Crabtree effect, followed by oxygen breathing (27). Given the pleiotropic effects of glucocorticoids on oxygen consumption, perfusion, and red cell viscosity as indicated in this current paper and elsewhere, it makes sense to use steroids in combination with hyperoxic gases and/or ET-1 antagonists.

Jain has discussed the concept of vascular normalization following the administration of vascular endothelial growth factor antagonists, which is accompanied by the reduction in vascular diameter and dropout of more immature vasculature (28). A more efficient vasculature could exhibit a lower overall perfusion rate and yet improve oxygen and drug transport. The effects of steroids on angiogenesis need to be considered in this context. The improvements seen in this paper on oxygenation...
were quite rapid, but the effects of steroids, in general, persist more than a few minutes. Over a fractionated course of radiotherapy, patients would be exposed to the drug over many days. Yano et al. recently reported that dexamethasone can inhibit vascular endothelial growth factor and interleukin-8 expression in prostate cancer cells by binding to the glucocorticoid receptor (29). These effects occur within 2 h after exposure to the drug. When given in vivo, dexamethasone caused a reduction in vascular endothelial growth factor, interleukin-8, vascular density, and tumor growth rate. Not all tumor cells express glucocorticoid receptors, but macrophages, which can comprise a substantial fraction of tumors, contribute to angiogenesis and express such receptors (30, 31). Therefore, it is anticipated that steroids may influence angiogenesis in many tumor types.

It is important to consider whether steroid use throughout a course of fractionated radiotherapy is practical. For brain tumors, chronic steroid use is routinely practiced to assist in reducing edema. Whether or not their use improves radiotherapy response cannot be tested in this site. In other types of solid cancers, steroids are used intermittently, primarily as antiepilogue, when radiotherapy is combined with chemotherapy (32). Dosing of these drugs is crucial. In one clinical report, administration of high-dose steroid tapers led to an unacceptable frequency of severe complications and even death, when combined with radiotherapy (33). Clinical trials could be developed, perhaps starting first with designs to test whether moderate steroid doses improve oxygenation after a single treatment, before launching into larger scale trials. Chronic steroid use also has potential negative effects. Yeast infections can occur as a result of depressed immune function, and other Cushingsoid symptoms may contribute to morbidity. Avascular necrosis of the femoral head has also been found following steroid use (34, 35).

In summary, despite decades of work, no single method for improving tumor oxygenation has emerged that is both effective and clinically practical. However, multifaceted strategies that simultaneously address two or more of the factors that determine tumor oxygenation show promise, particularly if reduction of oxygen consumption is part of the strategy. Thus, the use of corticosteroids as suggested here by Crokart et al. (1) could be considered as part of a multifaceted approach to improve oxygenation and radiosensitivity.

References
