EDITORIAL

Photodynamic Therapy—Lots of Questions But Presently Few Answers

Eli Glatstein

The elimination of malignancy is the ultimate oncologic goal. Many tumors can be killed by large amounts of chemotherapy or ionizing radiation. Unfortunately, host tolerance to treatment frequently limits the extent to which these modalities can be used. Therefore, skilled use of effective but nonselective modalities is the present basis of oncology.

The recent clinical interest in the use of photodynamic therapy (PDT) for tumor treatment rests on preferential retention of selected sensitizers within tumors (1). Although PDT has been used to treat over 3,000 patients, the modality is still experimental, and the exact means by which certain sensitizers are selectively retained in tumors and the mechanism by which a tumoricidal effect results are not certain. PDT is differentiated from therapies like psoralen plus UVA-based phototherapies because during tumor treatment PDT requires the presence of three components: oxygen, light, and sensitizer. Hence, PDT is a photo-oxidative process.

At least one in vivo and three in vitro studies (2,3) demonstrate the requirement of oxygen in PDT that is based on a hematoporphyrin derivative (HPD). The oxygen concentration required for PDT is tenfold greater than that found for the ionizing radiation. Furthermore, even though oxygen enhances effectiveness by a factor of three when ionizing radiation is used, there is still a tumoricidal effect in the absence of oxygen. This is not true for PDT; relative hypoxia, i.e., less than 1%, results in the absence of a therapeutic effect. Also, ionizing radiation and photodynamic radiation therapy differ in the means by which oxygen interacts with radiation. Highly reactive, oxygen-derived free radicals are produced with ionizing radiation; whereas, for PDT a sensitizer dye such as HPD is first excited by visible light, then energy is transferred from the excited sensitizer to oxygen to produce singlet oxygen, which subsequently reacts with vulnerable cellular targets. For ionizing radiation, the vulnerable target is usually considered to be DNA; for PDT, cytoplasmic, nuclear, mitochondrial, and organelle membranes appear to be the targets. By virtue of DNA damage, ionizing radiation-induced cytotoxic effects are usually not evident until cells divide. In contrast, PDT tumoricidal effects are usually considered rapid and independent of cell division. In both cases, cellular repair mechanisms can be operative, and therefore effects of dose rate can be seen and may have important clinical ramifications.

The first clinical use of HPD was not for treatment but for diagnosis of malignancies by direct visualization. The reason is simply that HPD, as has been subsequently shown for phthalocyanine and many other porphyrin-based dyes, apparently is selectively retained within tumors. The basis for this relative tumor retention of sensitizer is not understood and is the subject of intense research. Explanations such as "leaky" tumor neovasculature creating greater sensitizer permeability, tumor production of bradykinins with resultant increased sensitizer permeability, greater HPD-protein carrier receptor sites on tumors, and poorly developed tumor lymphatics resulting in slower clearance of the sensitizer from the tumor site have all been suggested responsible for selective sensitizer retention. In vitro studies thus far have not been helpful in elucidating the reason(s) for in vivo tumor retention. In the in vitro setting, with few exceptions, there is no indication that malignant cells take up or retain more sensitizer than do normal cells. It is obvious that physiologic processes are dictating in vivo tumor-specific accumulation of the sensitizer. Without question, the chemical characteristics of the sensitizer determine the physiologic behavior. This is most apparent when considering HPD, which is made from hematoporphyrin, and both have in vitro tumoricidal activity. Yet in in vivo experiments, only the derivative is selectively retained and therefore useful for PDT. Possibly the work presented in this issue addressing the in vivo site of action of PDT will also extend our knowledge, not only in area of the mechanism of PDT action but also to the means by which sensitizers are selectively retained by tumors.

Previous experiments performed by Bugelski et al. (4) had indicated that early and brisk endothelial damage is partly responsible for the tumoricidal effectiveness of HPD-based PDT. Subsequently, Henderson et al. (5), using a murine in vivo/in vitro tumor model, showed that PDT induces hypoxia and the acute hypoxia presumably results in tumor death. Endothelial cell damage, by virtue of being responsible for vascular integrity and the macroscopic conduit of oxygen, seemed to be the most apparent target and explanation of the results. However, it seems just as plausible that damage to the endothelial basement membrane or the matrix material juxtaposed to basement membrane could result in vascular damage and a subsequent "no flow state" and induction of anoxia. Certainly in other diseases, damage to the basement membrane results in tissue damage and cell death. What is not totally clear at this time is an explanation of the observation that at clinically useful light doses at which temperature effects are minimal, blood flow to the tumor, as monitored by laser Doppler measurements, may actually increase for a short time during and after therapy, followed thereafter by a marked reduction in blood flow (6). Does such a transient blood flow increase indicate damage to the endothelial surface with resultant release of vasoactive substances? Is the consequence of such increased blood flow responsible

Received November 10, 1988; accepted November 10, 1988.

Radiation Oncology Branch, Division of Cancer Treatment, National Cancer Institute, Bldg. 10, Rm. B3B38, National Institutes of Health, Bethesda, MD 20892.
for signaling release of factors that in some way impact on tumor kill? Additionally, although acutely induced hypoxia might be responsible for the majority of tumor death induced by PDT, what is responsible for the death of tumor cells residing at the edges of tumor masses where intimate contact with tumor vessels for nutrients is not apparent? Do such cells die because of damage to surrounding normal tissue vasculature? Likewise, does the failure of tumors to respond to PDT mean that the vascular network within and around the tumor is resistant to PDT damage? If vascular infarction is the aim, why is there a need for selective retention of dyes? Would not light delivered specifically to the tumor and surrounding area be just as effective if the sensitizer were equally distributed throughout all blood vessels within the body? If that were the case, then dyes with specific affinity for the vascular network should be sought more diligently. Then, of course, could two, or more, in vivo tumoricidal mechanisms of PDT be operative? One result could depend on vascular collapse, whereas the other could be from direct PDT tumor kill. That is, are there direct and indirect PDT effects? Answers to such questions will undoubtedly be forthcoming from continued, exciting basic science research as long as PDT continues to be an effective treatment modality.

It is generally acknowledged that when enough light and sensitizer can be delivered, PDT is an effective local tumor treatment modality for superficial tumors. New sensitizers with properties that will allow use of longer wavelength light for greater tumor penetration should extend the application and efficacy of PDT. A more thorough understanding of the mechanisms by which PDT actually works for individual sensitizers in vivo conditions should afford researchers the opportunity to modulate the PDT effect and should augment skills for those using PDT for tumor treatment.

References