PHOTODYNAMIC THERAPY OF TUMORS

A REVIEW OF PDT DOSIMETRY

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I. INTRODUCTION

The field of photodynamic therapy (PDT) has been the subject of a number of recent comprehensive review articles. The aim of this chapter is to deal in some depth with the dosimetry of PDT.

PDT is an experimental cancer treatment. It consists of an intravenous injection of the photo-sensitizing drug Photofrin II. The drug is retained by the tumor at a higher level than the surrounding normal tissue. 24 to 72 hours later the tumor and surrounding normal tissue are exposed to 630 nm light. This results in the selective destruction of malignant tissue. Significant levels of drug also are retained by cells of the reticuloendothelial system such as the Kupffer's cells of the liver and the macrophages of the skin and spleen. At the currently prescribed drug doses (1 or 2 mg/kg) this results in post treatment cutaneous photosensitivity of at least 4 to 6 weeks. Consequently the patient suffers the inconvenience of being forced to remain indoors during daylight hours for about one month. Drug de-escalation protocols are being carried out at Roswell Park as a part of phase two dosimetry studies. Although these studies are motivated by an attempt to improve the therapeutic ratio it is hoped that a peripheral benefit of lower drug dose will be a reduction in the severity and longevity of skin photosensitivity.

Since 1977 about 4,000 patients have been treated by photodynamic therapy. Most of this work has been on late stage patients and was palliative in nature. We are just beginning to see the results of the treatment of early stage lung cancer from Japan. A group at the Tokyo Medical College and one at the Mayo Clinic have data on a small but growing number of cases with a five years follow up.

Phase III trials (randomization of patients into a standard therapy or PDT) are underway. When the results of these studies are reviewed by the FDA the drug will no longer be restricted to experimental protocols and will be approved for routine use in oncology in the United States.

An application for regulatory approval has been filed with the Canadian Health Protection Board based on the accumulated clinical data in the treatment of lung and bladder cancer. A similar filing has been made in Sweden.
The effect of PDT (when the dosimetry is correct) is to cause the tumor tissue necrosis and spare the surrounding normal tissue although both receive the same light dose. Until recently the light dose which could be safely delivered was limited by normal tissue drug levels. This in turn limited the depth to which a satisfactory therapy could be delivered. The wish to improve the clinical results lead to a study of PDT dosimetry.

II. REVIEW OF THE DOSIMETRY LITERATURE

The development of PDT dosimetry has proceeded from purely empirical rules toward a theoretical framework relating the clinical parameters of injected drug dose and light dose to a predictable quantitative result. In the process insight into the physics of light propagation in tissues was necessary together with the relationship of tissue levels of sensitizer to injected dose.

The requirement for oxygen to be present for PDT to occur was demonstrated in mice. The detection of the 1.27 micron fluorescence from the radiative decay of singlet oxygen generated by PDT in a mouse has been reported. The measurement of singlet oxygen fluorescence is extremely difficult and has not as yet been reported by others.

Finally the biological response must be related to the effects produced by the combination of sensitizer and light. There is as yet no theoretical way to predict the response of tissue. Thus the dosimetry is only useful if we quantify theoretically the photodynamic dose used to achieve a measured biological end point (e.g. depth of tissue necrosis). Then we use this empirical response parameter (the minimum dose required to necrose tissue) in the theory to choose another set of drug and light doses which will reliably necrose tumor to any desired depth (assuming knowledge of the attenuation of the tissue and within the practical limits imposed by the penetration of light). This is useful because as we shall see different drug and light combinations which result in the delivery of the same dose to the desired depth are not equivalent at any other depth. This is true because of the effects of photobleaching. Photobleaching, the photo-chemical destruction of sensitizer, results in the limitation of the PDT dose in the tissue to a finite value which depends only on the amount of sensitizer present at the start of treatment and the bleaching rate (a single constant for all tissue).

III. LIGHT IN TISSUE

L. O. Svaasand was one of the first to recognize that because propagation of red light in tissues is dominated by scattering it is best described as a process of diffusion. The transport theory of Chandrasekhar has been extremely useful in the description of the diffusion of photons through tissue. The early European workers in this field tended to employ the Kubelka-Munk theory of light transport which had several disadvantages when dealing with this problem. It required the determination of light fluxes traveling in several directions in tissue which were not accessible to measurement. It has been recently demonstrated that the Kubelka-Munk parameters are connected to those of diffusion theory. The great advantage of diffusion theory is that it describes light transport using only two parameters, a diffusion coefficient and an absorption coefficient. These parameters are measurable by noninvasive techniques and can be determined in the clinical situation (see for example the References 12 and 13). Furthermore once the light is completely diffused (i.e. isotropic) as the result of multiple scattering is described by a single parameter, the total attenuation coefficient, which can be determined by the noninvasive technique described in Reference 14.