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HOW TUMOR-SPECIFIC CAN PHOTODYNAMIC THERAPY BE MADE?

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Purpose/Objective: As modern predictive assays reliably define solid tumors which are unlikely to respond to radiotherapy, alternative cancer treatments will be required. Our research has defined three different mechanisms for selectively targeting tumor tissue with photodynamic therapy (PDT). 1) The delivery of laser light with good uniformity to specific tumor volumes was previously reported. 2) The pharmacokinetics of three second-generation photosensitizers of pheophorbide and porphyrin base were measured to determine the time after drug administration when tumor/normal tissue levels are maximum. 3) Since tumor response to PDT is mainly by secondary ischemic cell death, the scheduling of adjunctive bioreductive chemotherapy with etanidazole and tirapazamine was investigated.

Materials and Methods: The second-generation photosensitizers, DR-5, Ph 4-OH and Toly-P, activated by 664, 670 and 681 nm light, respectively, were selected for these studies with EMT-6 tumor-bearing CB17/Icr *scid* mice. Tumor response to PDT was measured by growth delay assays as well as *in vivo/in vitro* assays of tumor cell clonogenicity. Drug delivery to tumor and eight different normal tissues was measured by spectrofluorometric analyses at various times after photosensitizer administration and tumor/normal tissue ratios of drugs were computed. The timing of etanidazole and tirapazamine administration prior to PDT treatment was investigated to determine maximum chemopotentiation of tumor response.

Results: DR-5, Ph 4-OH and Toly-P were found to produce dramatic tumor responses and cures when administered 1 hr prior to tumor illumination with laser light of specific wavelength. Toly-P was found to be a more potent photosensitizer *in vivo* than were DR-5 and Ph 4-OH. *In vivo/in vitro* assays of tumor cell clonogenicity indicated no direct tumor cell inactivation by these treatments. Tumor cell death occurred hours after tumor perfusion shutdown, presumably by secondary hypoxic death. Both tumor growth delay and the kinetics of tumor cell death will be reported for laser light administered at times when tumor/normal tissue levels of photosensitizers are maximum. PDT-induced tumor response was potentiated by etanidazole and tirapazamine. The optimum scheduling of bioreductive chemotherapy with PDT will be reported.

Conclusion: We previously described tissue illuminators consisting of laterally-diffusing optical fibers which produced relatively uniform light fields in solid tumors of different shapes and size. Tissue light intensities were accurately predicted by a 2-D photodosimetry code (T-PIPET). Our current studies have now defined the time after photosensitizer administration at which tumor/normal tissue drug levels are maximum and PDT effects in tumor tissue most selective. As well, bioreductive chemotherapy can potentiate the secondary ischemic cell death produced in tumors by the primary action of PDT on tumor vasculature. Since PDT inactivation of cells is by membrane damage and since PDT targets in solid tumors are endothelial cells, interstitial PDT should be an effective therapy for accessible radiation-resistant tumors whose radiosensitivity is determined by physiological, cell kinetic and genetic properties of tumor cells.

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IN VITRO MODELLING OF CONCOMITANT CISPLATIN/RADIOTHERAPY TREATMENT OF HUMAN CERVICAL TUMORS

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Purpose/Objective
Cisplatin is being increasingly used in combination with radiotherapy to treat carcinoma of the cervix. Although there is some evidence to suggest that cisplatin acts as a radiosensitizer in rodent fibroblasts, this has not been conclusively demonstrated in human tumor cell lines. We thus evaluated the effect of clinically relevant levels of cisplatin on the radiosensitivity of human cervical tumor cells, and estimated what changes in local control rates might be expected to accrue from the concomitant use of cisplatin during fractionated radiotherapy.

Materials and Methods
The effects of concomitant cisplatin (1 μg/ml, a typical intra-tumor concentration) on the clinically relevant radiosensitivity i.e. SF_2 values were determined in 19 cloned human cervical tumor cell lines under both aerobic and hypoxic conditions. These early passage cell lines had SF_2 values ranging from 0.2 to 0.8.

Results
The concomitant administration of cisplatin reduced the clinically relevant radiosensitivity in the majority (11/19) of the human tumor cell lines investigated. In only 4/19 was any radiosensitization observed, and in 4/19 cell lines there was no significant change in radiosensitivity. However, the sum of the independent cell killing by radiation and cisplatin was approximately 2-fold higher than after radiation alone. There was no apparent dependence of the cisplatin- induced changes in SF_2 values upon the level of cell killing by cisplatin. However, there is a suggestion that concomitant cisplatin administration may have a differential effect in inherently radiosensitive and resistant human tumor cell lines.

Conclusions
Our data suggests that concomitant cisplatin/radiotherapy regimens may result in a higher level of local tumor control, but primarily through additive toxicity and not through radiosensitization. Future improvements in local tumor control may thus be derived by increasing the total dose of cisplatin.