THEORETICAL BASIS AND CLINICAL APPLICATIONS OF
5-FLUOROURACIL AS A RADIOSENSITIZER

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INTRODUCTION

During the past 5 years several institutions have combined the anti-metabolite 5-Fluorouracil (5-FU) and radiation in the treatment of various human cancers. The results of these studies are thus far uniformly promising but as yet no randomized investigations have been conducted. The stimulus to these pilot studies came from two disparate sources. The first was the empiric observation by Nigro et al (23) that an infusion of 5-FU (combined with Porfiromycin or Mitomycin C), coupled in part with radiation, led to rapid pre-operative regression of squamous anal cancer. These results led to an application of this type of pre-operative program to other cancers (15, 17, 20, 26).

RADIOBIOLOGICAL BASIS OF 5-FU RADIosensitization

The second stimulus has been the identification of the scheduling requisites for the application of 5-FU as a true radiosensitizer (RS) of human tumors (7). 5-FU has been known to be a RS for about two decades. The RS properties of 5-FU were first demonstrated in tissue culture by Bagshaw soon after its introduction (2). Mouse leukemia cells were subsequently shown to be strikingly RS in vivo (29). These original pre-clinical studies stimulated a wealth of early clinical trials using various combinations of 5-FU and external beam radiation. Some of these early studies suggested clinical benefit, others did not. All employed bolus 5-FU, usually in some variant of the original Wisconsin regimen in which daily, bolus 5-FU to toxicity (usually myelosuppression) was given followed by lower dose maintenance bolus 5-FU.

However, it was eventually shown in the author's laboratory (7) that bolus 5-FU cannot RS because of the pharmacological requirements of the RS phenomenon. Basically, the RS state is a cellular condition that develops gradually in the 24 hours or more after a radiation exposure. Moreover, it occurs only if the cell is exposed to an adequate concentration of 5-FU. Exposure of the cells to 5-FU prior to radiation has no sensitizing effect although additive toxicity (and tumor response) may occur. At the cellular level it appears likely that the...
radiation exposure may actually be sensitizing the cells to 5-FU (7,14).

Since tissues with slow turn-over times (nerve sheaths, vascular tissue, connective tissue etc.) are not affected by 5-FU, most late effects of radiation are not enhanced. Therefore full doses of radiation may be used provided appropriate adjustments in fractionation are employed to prevent serious epithelial damage that may itself lead to adverse late radiation effects.

We have also demonstrated that RS by 5-FU is not an arcane cellular event. It requires a substantial cytotoxic effect of the drug itself to become significant (7,14). In tissue culture this means RS is found only when there is sufficient drug (on a concentration x time basis) to produce a kill of about 30% of the cells without added x-rays (7). In terms of clinical applications, RS can probably always be anticipated if enough infused 5-FU is given to achieve a partial response (i.e. a PR without any added x-rays). This supposition will hold provided the tumor is not intrinsically radioresistant since in such cases RS by 5-FU seems unlikely. Clinically, this makes 5-FU RS therapy most useful in epithelial tissues which are sensitive both to 5-FU and radiation. Since the quantitative cytotoxicity of 5-FU is usually not first estimated in a clinical trial the administration of each 5-FU infusion to clinical toxicity is theoretically desirable (7,12).

The exact reasons that bolus-equivalent 5-FU does not RS are not known. It may well stem from the mode of action of the drug in some cells. Infused 5-FU may poison some types of tissues (and their derivative cancers) through its accumulation in cellular RNA rather than the more commonly proposed mechanism of inhibition of thymidylate synthetase (1,14,18). This interpretation is consistent with both the temporal sequence for RS (drug after x-ray) and the relatively slow development of RS in irradiated cells.

CLINICAL SCHEDULING REQUISITES OF 5-FU RS

Once it was understood that RS required a significant period of time to develop, it became apparent that only slowly infused 5-FU could RS. This stems from the short half-life of 5-FU in the bloodstream. When 5-FU is administered as a bolus injection its half life in the blood is only about 10 minutes with most of the drug being rapidly degraded by the liver (22). In order to create the conditions required for RS (a reasonably constant exposure to extra-cellular 5-FU for about 24 hours after each radiation exposure), it is necessary to constantly renew the internal supply of drug. Currently, this can only be done adequately by a slow, continuous infusion. Accordingly, the clinical toxicity of slowly infused becomes quite relevant.

The importance of scheduling in the normal tissue sensitivity to 5-FU was first pointed out by Seifert et al (25). They showed that the limiting toxicity of 5-FU reversed itself when the schedule of administration was changed from bolus to a 5-day infusion. During bolus 5-FU therapy bone marrow toxicity is almost always limiting, and is sometimes lethal (25). However, when a 5-FU infusion is given for 4-5