21 Protracted (Continuous 5-Fluorouracil) Infusion with Concomitant Radiation Therapy: Indications and Results

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21.1 Introduction

The favorable therapeutic exploitation by the combination of two cytotoxic agents, namely ionizing radiation and an antimetabolite, in this case the fluorinated pyrimidine, 5-fluorouracil, (5-FU), has been attempted over the past 25 years with variable success. After the discovery of a synergistic effect on cancers in laboratory animals by this combination therapy (HEIDELBERGER et al. 1958), clinical trials in the early 1960s with 5-FU and radiotherapy showed only moderate success, and in some trials there was no superiority over irradiation alone. Nevertheless, investigation continued until the pioneering work at the Mayo Clinic (MOERTEL et al. 1969) which provided the guidelines for the maximum permissible dose of 5-FU administered by rapid intravenous injection with radiotherapy. Clinical studies using these guidelines ensued in the 1970s and 1980s and a majority of the nonrandomized and randomized trials for patients with adenocarcinomas of the gastrointestinal tract demonstrated a benefit in local control and survival for those receiving chemoradiation (SCHIN et al. 1982). More recently, interest has grown in using 5-FU given as a continuous infusion employing either short (96–120 h) or protracted (more than 30 days) infusion schedules combined with conventionally fractionated irradiation ("chemoradiation") (RICH et al. 1985b). In this chapter, emphasis will be placed on the use of protracted infusion 5-FU in the Department of Clinical Radiotherapy at M.D. Anderson Cancer Center (MDACC), Houston, Texas.

21.2 Background

Over the last decades, several technical innovations have made the use of continuous infusion clinically practical. The use of Silastic catheters that are inserted into the extremity or placed in the subclavian vein permits long-term vascular access (BOTE and DALY 1987). Techniques are now standardized that allow safe, convenient, and low cost intravenous administration of a variety of chemotherapeutic agents. A second technical innovation that has permitted outpatient continuous infusion chemotherapy programs to flourish is the development of the low cost ambulatory infusion pump. Electrical mechanical devices are available that permit programmable, intermittent infusion as well as continuous infusion schedules (TUCKER 1987). At MDACC, a balloon pump housed in a plastic cylinder was developed in conjunction with the Travenol Corporation. The pump is small, lightweight, and can be worn under the clothing very easily. The pump is self-contained,
and depending on the chemotherapeutic agent can be prepared several days in advance so that the patient can exchange a new pump daily at home. A typical course of continuous infusion chemotherapy combined with radiotherapy for 5–6 weeks will cost approximately $900–$1000 for the infusors.

21.2.1 Background Studies Using Low Dose Continuous 5-Fluorouracil Infusion for Patients with Gastrointestinal Cancers

The mainstay of chemotherapy for patients with advanced adenocarcinoma of the gastrointestinal tract has been 5-FU over the last 25 years. As a single agent, it appears to have produced a consistent objective response rate of 8%–20% when given as bolus injections. In an effort to overcome chemotherapy resistance, drug administration by continuous infusion schedules has been tried with variable success. Relatively short infusion schedules of 8–24 h did not show any significant improvement in responses in patients with advanced colorectal cancers (O'CONNELL 1987). More recently, interest in protracted infusion schedules greater than 24 h have been tried. LOKICH et al. (1981) have reported on a phase I study using continuous venous infusion of 5-FU given for protracted periods through central venous catheters using ambulatory pumps. The initial report showed a dose-limiting toxicity of stomatitis at a daily dose of >300 mg/m²/day for period of only 8–23 consecutive days. When doses of <300 mg/m²/day were used, it was possible to administer continuous infusion 5-FU for as long as 60–90 days without significant toxicity. The cumulative doses of 5-FU can be three to four times greater than that achieved by bolus or 5-days infusion schedules. The main toxicity encountered when patients receive low dose continuous 5-FU (>30 days) generally consists of mucocutaneous reactions, most notably stomatitis. Patients may also experience redness and swelling of the distal fingers, palms, and soles associated with paresthesias and a burning sensation referred to as the “hand-foot syndrome.” Gastrointestinal toxicity consisting of nausea, vomiting, and diarrhea may also ensue, especially in patients receiving concurrent external beam irradiation to the abdomen or pelvis.

In 1985, we reported on the initial experience using low dose 5-FU infusion and concomitant radiation therapy (RICH et al. 1985b). A total of 41 patients were evaluated at the New England Deaconess Hospital (NEDH), Boston, Mass. The tumor sites were esophagus (9), bile duct (3), pancreas (9), stomach (9), colon (5), rectum (5), and anus (1). Most patients had unresected disease or a high risk of residual disease after resection at the time of referral for irradiation. A 5-FU dose of 250–300 mg/m²/24 h was infused at rates of 9–12 ml/day.

Cumulative 5-FU doses ranged from 4.6 to 48.2 g (median 14.5 g given over 34 days). An additional infusion of 5-FU or other cytotoxic drugs was used either before or after chemoradiation in 20 patients.

Total radiation doses were planned in most cases to deliver 40–50 Gy for patients receiving adjuvant treatment, and up to 60–70 Gy for those with unresected disease. Irradiation was generally delivered at a rate of 1.8–2 Gy per day although several patients who received palliative radiotherapy (XRT) had fraction sizes of 2.5–3 Gy per day. The median duration of therapy was 5 weeks, which closely coincided with the median duration of 5-FU infusion.

Some toxicity was encountered in all patients. The major categories were gastrointestinal and mucocutaneous reactions with a minority having any hematological toxicity. Acute toxicity was considered mild in 27 patients (66%) and consisted of dysphagia/stomatitis, nausea, and diarrhea. These symptoms were controlled adequately with analgesics, antiemetics, and anticholinergics so that cessation of chemotherapy or radiotherapy was not required. In five patients, additional manifestation of toxicity were conjunctivitis and a macular skin rash. Moderate toxicity was observed in any patient having symptoms not adequately controlled with medications. Stomatitis occurred in nine patients, resulting in temporary interruption of 5-FU, and in five of these the total 5-FU dose given was less then 10 g. Temporary interruption of treatment because of difficulty in controlling nausea and diarrhea occurred in three other patients. Severe toxicity requiring cessation of all therapy occurred in two patients (5%). Both patients had circumstances unrelated to the combined modality therapy which could have also lowered the acute tolerance. Lastly, another toxicity was symptomatic venous thrombosis in three patients (7%), which precluded further chemotherapy. Low hematological toxicity was