Modulation of Dose Intensity in Aerodigestive Tract Cancers: Strategies to Reduce Toxicity

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Advances in diagnostic and therapeutic radiology and a better understanding of cell biology are being applied in practical ways to modulate treatment morbidity. Conformal radiotherapy targets the cancer precisely and can be combined with new systemically administered radiosensitizers.

Treatment advances in upper aerodigestive tract cancers using altered radiotherapy fractionation in multiple daily vs once daily doses underscores the importance of the temporal pattern of dose administration. Accelerated or hyperfractionated irradiation schedules result in improved survival and local tumor control in patients with head and neck and esophageal cancers.[1-3] This finding supports further evaluation of compressed treatment schedules to attack accelerating repopulating tumor cells,[4,5] or "regenerative resistance."[6] Schedules that provide higher dose intensity (accelerated irradiation) or higher dose density (sequential chemotherapy delivered in short overall time spans) are associated with successes in radiation and medical oncology, respectively. These intense weekly or high total doses can increase the incidence of acute complications, however, as predicted by laboratory and clinical models.[7]

A parallel exists between this increased morbidity and the morbidity associated with chemoradiation, where concurrent irradiation is combined with simultaneous anti-S-phase radiosensitizing chemotherapy[8] (frequently fluorouracil [5-FU]-based), and cure rates in gastrointestinal (GI) cancers have increased (esophageal, gastric, pancreaticobiliary, rectal, and anal).[9-11] One underutilized approach to better leverage outcomes for these cancers is to identify ways in which to widen the therapeutic window by reducing acute complications.

This review discusses several of these methods, focusing on the temporal pattern of radiosensitizing chemotherapy administration during radiotherapy, so as to ameliorate the GI toxicity of aggressive chemoradiation by exploiting the differential temporal sensitivity of normal tissues to cytotoxic insult (Figure 1).

New Radiotherapy: 'Find the Tumor, Hide the Dose'

Better local cure is being attempted through improved tumor definition coupled with altered fractionation (thereby increasing radiotherapy dose intensity), or by the delivery of ultrahigh total doses through computer-controlled treatment approaches.[12] Computerized tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) are used to delineate precisely the extent of local and regional disease.[13] These diagnostic radiology approaches are used with three-dimensional (3D) treatment planning systems to allow dose "sculpting" or isodose "painting" and tightly conform treatment to the anatomic disease process. Until prospective randomized trials are conducted, the full value of these new technical approaches in terms of improved tumor control rates, with or without acceptable normal tissue toxicity, will remain unknown.

Nevertheless, early results with conformal therapy (including intensity-modulated radiation therapy) suggest that morbidity is decreased, compared to standard treatment. For example, with CT treatment planning, radiation dose distributions can be designed that envelop a head and neck cancer while transit doses avoid the parotid glands, thereby reducing xerostomia.[14] For prostate cancer, where the use of total doses of 80 Gy or more suggest better local control in nonrandomized studies, the anterior rectal wall can be spared acute damage with similar techniques.[15] For tumors of the upper GI tract, doses of 60 to 72 Gy have been used for hepatic[16,17] and pancreatic cancers[18] without incurring excessive morbidity. One drawback associated with the use of these techniques, especially in the chest and abdomen, is that breathing may cause unwanted movement of the target, and without sophisticated gated radiotherapy,[19] a portion of the target area may be underdosed.
Despite this problem and other hurdles, the potential benefits of conformal radiotherapy include increased local cure rates, better control of regional micrometastatic disease (so-called oligometastasis), and better local symptom control because of tighter isodose distributions. Preventing acute normal tissue reactions could, in turn, allow more intense or dose-escalated concomitant radiosensitizing chemotherapy with less chance of a detrimental interruption in treatment.[20] Conformal treatment also requires more time for planning and implementation and can be more expensive than standard treatment, thus adding another question to be addressed in prospective trials.[21]

**Protecting Against Acute Reactions**

Acute reactions in the rapidly dividing tissue compartments of the aerodigestive tract mucosa or the parotid gland can also be protected from radiotherapy with chemical radioprotectors. The incidence of stomatitis and xerostomia can be reduced with the use of amifostine (Ethyol), a sulfhydryl radioprotector that acts to scavenge free radicals, and thereby, preferentially reduce the amount of initial radiation damage in normal tissue.[22] Although tumor protection has been a concern, clinical trials to date have not demonstrated any evidence in support of this activity. Another agent used successfully to ameliorate xerostomia is pilocarpine (Salagen), which is administered orally during and after irradiation.[23]

A third means of protecting normal tissues is with biomolecularly designed growth factors that alter mucosal proliferation (eg, keratinocyte growth factors).[24] These molecules have been evaluated in preclinical models, and clinical data should become available soon. One drawback to using chemical and biomolecular protection of normal tissues is the need to administer these agents with each radiation treatment, thus requiring technical staff to coordinate administration of additional treatments in conjunction with irradiation.

**Controlling Toxicity**

Increased toxicity has also been observed in the GI tract and bone marrow with chemoradiation compared to radiotherapy alone in gastric, pancreatic, biliary, rectal, and anal cancer.[25] Within this framework, when radiosensitizing chemotherapy is administered as a protracted venous infusion, compared to a rapid (bolus) injection, such treatment results in a different array and intensity of acute toxicities that can be exploited therapeutically (Figure 1). For example, myelosuppression is generally absent with protracted venous infusion of 5-FU chemoradiation but diarrhea is more common, partly because of the high cumulative doses administered during a course of pelvic irradiation.[26] Late morbidity is not increased, however, resulting in an overall therapeutic gain.[27]

To increase cure rates further among GI cancer patients will likely require the use of combinations of irradiation with newer systemic chemotherapeutic radiation sensitizers. There have already been reports of increased acute morbidity with taxanes,[28] gemcitabine (Gemzar),[29] and irinotecan (CPT-11, Camptosar)[30] combined with irradiation. These combinations may increase tumor cure but at the price of increased toxicity, because cellular damage in the highly proliferative GI tract can result from overlapping toxicity. Chemoradiation is similar to accelerated treatment in that the increased dose intensity[8] causes acute reactions to be more severe and appear sooner,[31] compared to irradiation alone.[32]

**Temporal Dose Intensity and Nonlinear Biology**

Chemoradiation-related aerodigestive toxicity (mucositis, esophagitis, and diarrhea) occurs because of the cell-cycle specificity of chemotherapy and the high proliferation rate of the aerodigestive tract mucosa. Newer evidence suggests that the expression of acute mucosal toxicity may be nonlinear and correlated with cell-cycle distribution over a 24-hour period. This implies that a temporal pattern of administering systemic radiosensitizing chemotherapy can be exploited to ameliorate acute toxicity. Although this concept is not new, recent laboratory and clinical experience suggests that it should be explored further in the clinic.

**Rhythmic Cell-Cycle Dynamics**

The daily cyclic patterns of mitosis in the GI mucosa are well known, but this relatively short phase of the cell cycle can be hard to detect and define precisely in terms of peaks and nadirs.[33] Mucosal proliferation can be measured more precisely in studies incorporating labeled thymidine ([³H]TdR DNA labeling index), which is circadian dependent.[34] Proliferation rates measured with the incorporation of labeled thymidine and, more recently, bromodeoxyuridine[35-37] in different portions of the mouse aerodigestive tract generally show peak DNA synthesis (acrophase) during the activity phase (Figure 2).[38]

In the mouse, functional activity of brush-border enzymes in the epithelial cells of the small intestine...
also shows significant circadian rhythm, and is influenced by changes in the light/dark cycle and the feeding schedules associated with activity.[39] Likewise, in humans, the rectal mucosa proliferation acrophase occurs at around 1:30[40] or 8 (Figure 2).[41] Similar circadian proliferation has been found in the bone marrow, where DNA synthesis displays a rhythmic behavior in both rodents and humans.[42] Although human data on this activity are sparse because of the difficulty in obtaining these measurements, when combined with the plethora of mouse data there is strong support for the concept of coordinated, rhythmic, nonlinear, cell-cycle dynamics in the human aerodigestive tract (Figure 2).

**Genetic Control of Circadian Rhythm**

The molecular biology of rhythmic proliferation in the human oral mucosa shows a significant circadian effect on the nuclear expression of cell-cycle checkpoint proteins (Figure 2).[43] Buccal mucosa biopsies obtained every 4 hours show significant variation in the maximal staining pattern of p53 in the morning (11 AM), indicating late G1 phase. This is followed 4 hours later by a peak in cyclin E (G1/S border) and 5 hours later by a peak in cyclin A, a G2 marker; the expression of cyclin B1 (a marker of mitosis) peaks in the evening at 8 PM. These data indicate genetic control of circadian rhythm and should be viewed in conjunction with the growing knowledge of the molecular biology of cell timekeeping pathways that are conserved in molds, drosophila, and mammalian cells.[44,45] The emerging picture shows autoregulatory transcriptional and translational feedback loops that have both positive and negative elements.[46] The positive components are two basic helix-loop-helix PAS-containing transcription factors—Clock and BMAL-1 proteins—which form dimers that bind to a DNA promoter sequence.[47] This, in turn, activates transcription of the Period and Cryptochrome genes, whose products act in the negative portion of the loop. These findings provide a molecular understanding of the clock mechanism of cellular circadian behavior.

The therapeutic consequences of this model may range from the identification of specific targets in a cancer cell’s "clock" to broader application of this knowledge in regard to optimizing the scheduling of cytotoxic or biological interventions. The latter concept, termed chronotolerance, provides the rationale for prospectively testing the administration of radiosensitizing chemotherapy with radiotherapy at the "best tolerated time" (Figure 2).

Empirically observed normal tissue chronotolerance in animals treated at different times can also be explained, in part, by circadian pharmacologic/pharmacokinetic differences in drug anabolism and catabolism.[48,49] For example, significantly less toxicity develops in mice when 5-FU is administered during the rest period compared to other times.[38,50,51]

**Studies of Chronotolerance**

Chronotolerance of the fluoropyrimidines has been studied extensively because these agents are commonly used in the treatment of GI tract cancers, with and without irradiation. The enzymes involved in the anabolism of 5-FU, including uridine phosphorylase, orotate phosphoribosyltransferase, and thymidine kinase (TK), have circadian patterns of peak activity.[51] Moreover, the predominant enzymatic pathway of catabolism, dihydropyrimidine dehydrogenase (DPD) exhibits marked circadian rhythmicity,[51] and DPD activity is inversely related to anabolic enzymes like TK.[52] These studies have been confirmed in humans receiving protracted venous infusions of 5-FU for measurement of DPD activity in peripheral blood mononuclear cells and in plasma.[53]

Chronotolerance may also provide an opportunity to escalate doses of cytotoxic chemotherapy that could potentially improve outcome. Animal tumors treated with cytotoxic drugs that are administered at differing times of day show enhanced cytotoxicity with chronomodulated administration schedules. For example, the alkylating agent cyclophosphamide (Cytoxan, Neosar) demonstrates significantly different activity when administration is coordinated with the mitotic index of the host bone marrow.[54] Between 12 noon and 4 pm, when the tumor mitotic index was high, a significant time-dependent tumor response was observed, compared to administration when the mitotic index was low (10 AM to 12 PM). Likewise, cytarabine cured twice as many animals with L1210 leukemia when it was administered at the acrophase of tumor proliferation.[55] The ability to escalate doses of other cytotoxic agents based on chronotolerance has been demonstrated in a variety of animal tumors.[56]

*Animal Studies* In our laboratory, we showed that the S-phase agent, 9-aminocamptothecin, a topoisomerase I inhibitor, displays marked chronotolerance.[57] In mice treated with intraperitoneal injection of 9-aminocamptothecin given at six different times—10 AM, 2 PM, 6 PM, 10 PM, 2 AM, and 6 AM—acute toxicity (weight loss, diarrhea, peripheral leukocyte counts) was lowest at 10 AM, 2 PM, and 6 AM, corresponding to the rest phase of the mouse circadian cycle.[57] Survival of mice treated at 2 AM decreased significantly compared to mice treated at 2 PM (eg, 90% survival at 2 AM vs 15% at 2 PM, *P* <
Irinotecan similarly displayed circadian cytotoxicity in BDF2 and ICR mice,[58] with toxicity markedly increased in the midactivity phase (eg, 1 AM).[59] The probable reason for this is the observation that the peak labeling index in the mouse jejunum occurs at 1 AM, during the midactivity phase.[37] We have also demonstrated in our animal model that, because of chronotolerance, we could escalate doses of 9-aminocamptothecin by 30% when combined with irradiation.[28] These data are consistent with the findings of a phase I trial in which chronomodulated irinotecan was delivered at 5 am (late rest phase), and was associated with mild toxicity in patients with metastatic colorectal cancer.[60] These observations suggest that the therapeutic index of irinotecan as a radiation sensitizer could be improved if administered at the "best tolerated time."

Clinical Feasibility—Along with these laboratory observations showing clinical application, use of chronomodulated therapy has also become widely feasible. Ambulatory treatment with programmable pumps to deliver chronoregulated intravenous treatment is convenient, safe, and widely available. This treatment approach has been shown to be practical in the multicenter setting and at the community hospital level. Moreover, the emergence of new orally administered 5-FU prodrugs like capecitabine (Xeloda) may provide additional clinical scenarios in which evening administration schedules would be of benefit.

Impact of Chronotolerance on Clinical Outcome

The timing of radiation-sensitizing chemotherapy administration based on chronotolerance may play an important role in promoting chemoradiation programs. Support for this concept comes from several clinical trials of chemotherapy alone or when combined with irradiation. The most extensive data exist for chemotherapy alone. In a multicentered, phase III trial, chronomodulated infusional 5-FU plus leucovorin (peak doses at 10 PM), plus oxaliplatin (peak dose at 6 PM) was compared to flat infusion in patients with metastatic colorectal cancer.[61] A fivefold decrease in acute toxicity was achieved with chronomodulated chemotherapy, compared to the identical chemotherapy administered over 24 hours in nonchronoregulated infusions (89% vs 18%, respectively, \( P < .05 \)). The decreased toxicity was associated with significantly higher dose intensity during each course of treatment, resulting in an improved objective response rate (53% vs 32%, respectively, \( P < .05 \)), better CEA tumor marker regression, and better median survival (19 vs 14.9 months, respectively, \( P = .03 \)).

University of Florida Study

In a study conducted by the University of Florida, a chronomodulated sinusoidal continuous infusion of 5-FU was administered daily with radiotherapy.[62] Peak infusion took place at midnight and was accomplished with the use of a programmable ambulatory infusion pump. Doses of 5-FU began at 250 mg/m²/d and were escalated to 325 mg/m²/d. The preoperative doses of irradiation ranged from 45 to 55 Gy, and all 18 patients successfully completed a full course of radiation therapy without interruption. Subsequently, all patients had resectable disease for potential cure. The maximum tolerated dose of 5-FU was 275 mg/m²/d, and no patient experienced grade 3 or higher toxicity at this dose. This represents a 22% increase in dose, compared to the chemoradiation dosage of 225 mg/m²² determined in a large randomized trial.[26] Chronomodulated 5-FU chemoradiation produced a pathologic complete response rate of 28%, compared to 11% for historical controls. This represents a five- to sixfold increase in pathologic response seen in similar patients with stage T4 disease who had been treated with nonchronomodulated 5-FU infusional chemoradiation at M. D. Anderson Cancer Center (Table 1).[63]

University of Virginia Study

Chronomodulated 5-FU infusional chemoradiation (using a pulsed infusion of 5-FU at 10 PM) was also studied at the University of Virginia (Table 1).[64] Fluorouracil doses were similar to those administered in the University of Florida study, with 250 to 300 mg/m²/d given 5 days per week during irradiation. Among 13 patients with T4 (fixed) rectal cancer treated with preoperative 5-FU chemoradiation, no Radiation Therapy Oncology Group (RTOG) grade 3 or 4 toxicity was reported, and the pathologic complete response rate was 30%. In another group of 23 patients with pancreatic cancer, RTOG grade 3 or 4 nausea was observed in only 4% of patients, compared to the results of flat-infusional chemoradiation with 5-FU in similar pancreaticobiliary cancer patients who showed grade 3 toxicities or greater of 11% to 19%.[64] Late toxicity was no different in the groups examined.

Joint Center for Radiation Therapy Study

Pilot data from the Joint Center for Radiation Therapy in Boston also used chronomodulated 5-FU
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Infusional chemoradiation in a pilot trial in 11 patients, with 75% of the dose pulsed between 10 pm and 4 am, and the remaining 25% given over the remainder of the day.[65] Doses of 5-FU were 240 mg/m²/d each day for the duration of radiotherapy. The incidence of toxicity was low, with only a single case of grade 3 toxicity.

These limited pilot trials have used peak doses of 5-FU administered at 10 PM,[64] 12 AM,[62] and 2 AM.[65] All reports show excellent tolerance and possibly a more effective outcome, compared to flat-infusional 5-FU chemoradiation (Table 1).

The EORTC Trial

Based on these data, a phase II trial using chronomodulated chemoradiotherapy is being initiated by the European Organization for Research and Treatment of Cancer (EORTC) in patients with potentially resectable biliary carcinoma. This rare disease was chosen because preliminary data using flat-infusional 5-FU plus 50.4-Gy irradiation resulted in approximately a 30% pathologic complete response rate.[66] The EORTC trial will prospectively assess the use of chronomodulated 5-FU infusion at 4 am combined with 50.4-Gy irradiation, with the end points being complete pathologic response to preoperative treatment, toxicity, and feasibility in a multicentered setting.

The timing of radiotherapy in this protocol is specified for the morning (10 AM to 12 PM), based on the theory that the rapidly dividing normal tissues in the GI mucosa will be relatively radioresistant because they will be in S-phase. This concept is taken directly from human buccal mucosal biopsies,[43] which showed evidence that S-phase cell-cycle checkpoints are highest in the morning. When the cells are in mitosis later in the day, there may be more mucosal toxicity. These findings are also the basis for a prospective randomized trial being conducted by the National Cancer Institute of Canada to evaluate the relationship between oral mucosal toxicity and the timing of daily irradiation, given either in the morning or the afternoon (personal communication, G. Bjarnason, 2000).

Protecting Normal Tissues From Chemoradiation: An Economic Perspective

A comparison of the costs of different methods of ameliorating acute (and late) mucosal toxicity from chemoradiation is shown in Table 2. Several chemical agents seem to be able to protect the upper aerodigestive tract mucosa or the parotid glands from irradiation. There are also technical radiotherapeutic approaches that appear to spare acute (and late) morbidity, but for many institutions this will require outlays of additional capital to upgrade treatment planning systems. These treatments may also require additional personnel to conduct administration, thereby further adding to the cost.

Moreover, certain aspects of improved diagnostic accuracy for cancer with CT, MRI, and PET will also translate into increased costs (and revenues) to the health-care system. Nevertheless, conformal treatment planning, 3D therapy, and intensity-modulated radiotherapy are exciting possibilities that are being evaluated alone or in combination with chemoradiation programs. In comparison, the costs associated with choosing the "best tolerated time" model for the administration of radiosensitizing systemic chemotherapy are relatively low, providing an additional reason to study prospectively the use chronomodulated chemoradiation scheduling.

Summary

Medical and technologic methods are being used to protect normal tissues from accelerated irradiation or chemoradiation. Chronotolerance, a concept based on the observations of circadian variation in the proliferation of acute-reacting GI tract mucosa, provides a rationale for chronomodulated administration of anti S-phase radiosensitizing chemotherapy (eg, with 5-FU, capecitabine, or irinotecan) at specific times when large volumes of normal tissues can be spared. This knowledge is only beginning to be exploited in the clinic, and the results so far point toward continued investigation of the temporal pattern of systemic administration of chemotherapeutic radiosensitizers in order to ameliorate toxicity and maximize treatment effect. This approach may be especially suitable in the elderly and those medically unfit to withstand the insult of more traditional dose-intensive chemoradiation schedules.

Another advantage of this method, now being tested prospectively in pure chemotherapy trials, may be the ability to escalate doses of systemic radiosensitizing chemotherapy or to achieve more dose-dense treatment schedules. In addition, the cost of administering systemic chemotherapy at the "best tolerated time" may be especially attractive with an oral agent such as capecitabine combined with irradiation. Chronomodulated administration of radiation-sensitizing chemotherapy may contribute to chemoradiation treatment programs being used today, and there is ample
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evidence that this idea needs to be examined further in prospective clinical trials.

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