Phase I Trial of Radiotherapy Concurrent with Twice-Weekly Gemcitabine for Head and Neck Cancer: Translation From Preclinical Investigations Aiming to Improve the Therapeutic Ratio1,2

Aron Popovtzer*,3, Daniel Normolle*1,4, Francis P. Worden†, Mark E. Prince§, Douglas B. Chepeha§, Gregory T. Wolf§, Carol R. Bradford§, Theodore S. Lawrence* and Avraham Eisbruch*

*Department of Radiation Oncology, University of Michigan Hospital, Ann Arbor, MI; †Department of Biostatistics, University of Michigan Hospital, Ann Arbor, MI; ‡Department of Medicine, University of Michigan Hospital, Ann Arbor, MI; §Department of Otorhinolaryngology-Head neck Surgery, University of Michigan Hospital, Ann Arbor, MI

Abstract

BACKGROUND: Once-weekly gemcitabine concurrent with radiotherapy was highly effective in the treatment of head and neck cancer (HNC) but limited by high mucosal toxicity. Pre-clinical investigations suggested that delivering gemcitabine at substantially lower doses twice weekly during radiotherapy improved the therapeutic ratio. We sought to translated these preclinical findings to a phase I trial. METHODS: Twenty-five patients with non-resectable HNC were scheduled to receive gemcitabine twice weekly during the last 2 weeks (total 5 infusions) of hyperfractionated radiotherapy delivering 1.2 Gy twice daily to total 76.8 Gy. Tumor biopsies to measure active intracellular (phosphorylated) gemcitabine were planned after the first drug delivery. Patients were assigned to escalating dose cohorts using the Continuous Reassessment Method. RESULTS: Twenty-one patients evaluable for toxicity were divided into cohorts receiving twice weekly treatment with 10, 20, 33, or 50 mg/m2 gemcitabine. Dose-limiting toxicity was grade 3-4 confluent mucositis/pharyngitis, and the maximally tolerated dose (MTD) was 20 mg/m2. Median survival was 20 months, with no difference between cohorts receiving lower (10, 20 mg/m2) or higher (33, 50 mg/m2) gemcitabine doses. Tumor biopsies after the first drug delivery showed only a minority of tumor cells in the specimens. CONCLUSION: These findings validate preclinical models that show that gemcitabine is radiation sensitizer at doses far below those used for systemic chemotherapy. However, the improvement in the therapeutic ratio predicted from the preclinical study did not translate into a substantial relative increase in the MTD of the drug in the clinical phase I trial.

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Introduction

Improved tumor control rates have been documented using concurrent radiotherapy and chemotherapy in patients with squamous cell carcinoma of the head and neck (HNC) [1,2], at the expense of higher rates of acute and late toxicities [2–6]. Strategies to improve these results include the development of better radiosensitizers and better drug-radiotherapy delivery schedules. Our group has previously demonstrated that subcytotoxic concentrations of gemcitabine act as radiosensitizers in cancer cells [7]. Prompted by these findings, we conducted a phase I study in patients with nonresectable head and neck cancer [8]. Radiotherapy was combined with a weekly dose of gemcitabine starting at a cohort receiving...
300 mg/m²/week, representing 25-33% of the weekly dose used for gemcitabine monotherapy (1000-1200mg/m²/week). Although the tumor-control rates were very encouraging, treatment led to severe mucosal/pharyngeal toxicity warranting a dose de-escalation. Excess toxicity, especially severe dysphagia, continued to be observed even at weekly doses as low as 50 mg/m²/week [8,9]. We concluded that this toxicity, especially severe dysphagia, continued to be observed even at weekly doses as low as 50 mg/m²/week [8,9]. We concluded that this regimen resulted in an unsatisfactory therapeutic ratio and was therefore not recommended for further study. Similar findings of severe acute mucosal reactions were reported by other investigators testing weekly gemcitabine concurrent with RT for HNC, with recommended phase II doses of 50 or 100 mg/m²/week, representing < 10% gemcitabine dose delivered alone [10,11].

In an attempt to improve the therapeutic ratio of concurrent gemcitabine-radiotherapy, we tested fractionated radiotherapy concurrent with different schedules of gemcitabine in mice implanted with squamous cell carcinoma [12]. Tumor eradication rate was measured vs. the main toxicities found in the clinical study (lip mucositis and weight loss representing acute dysphagia in mice). The highest therapeutic ratio was achieved with a twice-weekly regimen of gemcitabine, at substantially lower doses than in the once-weekly regimen [12]. We have translated these results into a phase I study of gemcitabine concurrent with RT for locoregionally advanced HNC, which is the subject of this report.

On the basis of the preclinical study, we hypothesized that the maximum tolerated dose (MTD) of gemcitabine administered twice weekly concurrent with RT would be close to the MTD of the drug delivered alone twice-weekly: 75-90mg/m²/dose [13,14], allowing potential preservation of the tumor sensitizing properties of gemcitabine in a better tolerated regimen.

We have employed in this study several additional strategies to maximize the efficacy of the combined regimen. There is a theoretical advantage of treatment intensification with chemotherapy during the last weeks of radiotherapy, when accelerated tumor cell population growth is thought to take place, and clinical reports support the efficacy of such a chemotherapy “boost” [15–18]. We therefore opted to administer the twice-weekly gemcitabine during the last 2 weeks of the radiotherapy course. During this phase, radiation was delivered only to the gross tumor volume, intending to minimize radiosensitization of the normal tissue included in target volumes of subclinical disease treated prophylactically. In addition, radiotherapy was hyperfractionated, to gain potential tumor-control advantages [19]. We report here the results of a phase I translating our pre-clinical study, seeking the MTD of gemcitabine administered twice a week during the last 2 weeks of a hyperfractionated RT course for locoregionally advanced, poor prognosis HNC.

**Patients and Methods**

The trial was approved by the University of Michigan Institutional Review Board, and all patients signed Institutional Review Board–approved informed consent.

The study group consisted of patients over 18 years of age with biopsy-proven squamous cell carcinoma of the head and neck who were not candidates for surgery because the tumor was considered nonresectable by tumor-board consensus or resection was expected to result in unacceptable functional or oncological outcomes. Other inclusion criteria were Karnofsky status at least 70, life expectancy at least 6 months, and adequate bone marrow, kidney, and liver function. Patients with a history of previous head/neck radiation or chemotherapy were excluded.

Patients underwent a complete history and physical examination, baseline assessment of organ function, documentation of tumor location and size, and pregnancy test for premenopausal women. Radiologic evaluation included chest x-ray, head and neck CT or PET-CT, and in some cases, MRI.

Intensity-modulated radiotherapy (IMRT) was delivered according to previously published methods [20]. Hyperfractionated radiotherapy was delivered twice daily at 1.2 Gy per fraction, at least 6 hours apart, 5 days a week. For the purposes of this protocol, IMRT was delivered in two consecutive plans. Over the first 21 treatment days (initial phase), 50.4 Gy was delivered to all targets in 42 twice-daily fractions of 1.2 Gy each. On days 22-32 (radiation boost phase), during which gemcitabine delivery was planned, an additional 26.4 Gy was delivered to the primary tumor and gross nodal CTVs (CTV1s) at 1.2 Gy per fraction, twice daily. The total intended CTV1 dose was 76.8 Gy, delivered over 6.5 weeks (64 fractions in 32 treatment days). Doses were prescribed to planning target volumes consisting of 0.5 cm uniform expansions of the CTVs. Target inhomogeneity goals were 99%-107% of the prescribed doses.

Gemcitabine was infused IV over 30 minutes. Five infusions were planned twice weekly during the last 11 treatment days (the radiation boost phase), at least 2 days apart.

Toxicity was graded according to the World Health Organization (WHO) scale for hematologic toxicities and the Radiation Therapy Oncology Group (RTOG) scale for nonhematologic toxicities. Grade 3 or 4 toxicities that did not improve to grade 2 or less within 3 months were considered dose-limiting. Late grade 3 esophageal toxicity was considered dose-limiting if it did not improve to grade 2 or less following dilation. In the event of an acute dose-limiting toxicity, or toxicity that required dose-holding, the scheduled gemcitabine treatment was temporarily halted until toxicity declined to grade 2 or less; it was then resumed at the next lower dose level. Radiation continued without interruption unless there was grade 4 mucositis or skin desquamation that did not respond to supportive measures. In these cases, a break in radiation treatment was allowed.

Tumor biopsies to assess the intracellular levels of dFdCTP and dFdCDP, the active metabolites of the drug, were planned 2 hours after the first gemcitabine infusion on day 22. The assessment methods for intracellular phosphorylated metabolites have been detailed previously [8].

Follow-up was conducted 4 weeks after completion of therapy, including clinical assessment for toxicity, history and physical examination, laboratory evaluation of liver and kidney function and complete blood count. Thereafter, patients were evaluated for late toxicity and tumor status every 2 months during the first 2 years and then every 3 to 4 months. At 3 months after completion of treatment, tumor response was assessed by physical examination and CT or PET scans, in addition to direct endoscopy under anesthesia. Complete response was defined as the disappearance of all assessable disease at endoscopy and on images.

The trial was designed to estimate the maximally tolerated dose (MTD), defined as the dose associated with unacceptable toxicity in < 20% of patients. Using modified Continual Reassessment Method (CRM) [21,22], we allocated each tested dose to cohorts of at least 3 patients. The first cohort was assigned 10 mg/m² twice weekly. After toxicity was evaluated, the target dose was estimated from the accumulated data, and the next cohort was assigned the next estimated target dose (20 mg/m² twice weekly). This was repeated for doses of 33 and 50 mg/m² twice weekly.
The following escalation restrictions were applied: 1. Doses could be escalated only one level between cohorts. 2. Doses could be escalated only after a minimum of 3 patients had been observed at the next lower dose for a minimum of 4 weeks. 3. Doses could be escalated only if no acute toxicity of grade 3 or higher was observed at the end of the 4-week post-therapy observation period in the previous cohort. If at least one acute toxicity of grade 4 or more was observed in a cohort, dose escalation was held up, and the patients were monitored for at least 3 months after completion of therapy. If, at that time, any toxicity had not resolved to grade 2 or less, it was classified as a DLT. Exceptions were late grade 3 skin, subcutaneous, mucosa, or salivary gland toxicities which are expected to occur in most patients following high-dose radiotherapy alone. Any toxicity of grade 4 or more at any time was considered a DLT.

The trial was planned to accrue 24 patients who were evaluable for DLT. After the trial was closed, the dose-toxicity function was estimated by logistic regression on all evaluable patients. The target dose was calculated by inverting the dose-toxicity function at P(DLT)=0.2.

Overall survival is described using the Kaplan-Meier method. Data were statistically analyzed with the SAS and R computing packages.

Results
Thirty-one patients were registered for the study from 2003 to 2007. Three were disqualified because of an initial finding of distant metastases (2 patients) or previous chemotherapy (1 patient), and 3 withdrew consent after accrual, for a final sample of 25 patients. Patient and tumor characteristics are detailed in Tables 1 and 2. The trial was aimed at patients with nonresectable squamous cell carcinoma. Reasons for nonresectability were carotid artery involvement by metastatic lymph nodes (16 patients), extensive infratemporal fossa and pterygoid plate involvement (4 patients), nasopharyngeal involvement by tonsillar cancer (3 patients), splenoid sinus involvement (one patient), and fixed tongue with bilateral hypoglossal nerve involvement (one patient). All patients with oral cavity, laryngeal, or hypopharyngeal cancer and 8 of the 10 patients with oropharyngeal cancer had a history of heavy smoking (>20 pack-years).

All 25 patients completed the chemoradiation protocol. Four were not evaluable for DLT owing to progressing local disease (3 patients) or death from uncontrolled diabetes 2 months after completing treatment (one).

Drug therapy was delivered as intended in almost all cases. One of the 5 intended doses was omitted in each of 7 patients receiving 20 mg/m²/wk, and in 2 of the 3 patients receiving 33 mg/m²/wk, because of severe mucositis. In 2 of 4 patients receiving 50 mg/m²/wk, the last dose was omitted because of severe mucositis. None of 6 patients treated with 10 mg/m²/wk required a drug-dose modification. Radiation therapy was delivered as intended to all patients, with no breaks short of holidays.

Table 3 shows the commonly observed acute and late toxicities and the DLTs at each dose level. Confluent acute mucositis and pharyngitis (RTOG grade 3) occurred in most patients, including those receiving the lowest dose of gemcitabine. Hematological toxicities occurred in only one patient. High-grade (RTOG grade 3 or more) late pharyngeal or skin toxicities occurred in 2/6 patients receiving 10 mg/m² and both occurred frequently in the patients receiving higher drug doses: 4/8 patients in the 20 mg/m² cohort, 2/3 in the 33-mg/m² cohort, and 3/4 in the 50-mg/m² cohort.

DLTs were documented in 6 patients: 2/8 patients in the 20 mg/m² cohort, 2/3 in the 33-mg/m², and 2/4 in the 50-mg/m² cohort. None of the patients receiving 10 mg/m² had a DLT. The dose was escalated from 33 mg/m²/wk to 50 mg/m²/wk because the adverse events in the 33-mg/m²/wk cohort were re-graded to DLTs after the dose in the 50-mg/m²/wk cohort had already been assigned. Five of the six patients with DLTs had mucosal and/or pharyngeal DLTs consisting of persistent deep ulceration in non-tumor-bearing areas, or pharyngeal/upper esophageal obstruction that could not be relieved by esophageal dilatation and required persistent gastric tube feeding. The remaining patient had an acute hematological toxicity (low neutrophil count).

Toxicity estimates using the CRM formula (which assumes a continuous dose-risk relationship) were 0.13 for 10 mg/m², 0.19 for 20 mg/m², 0.24 for 33 mg/m², and 0.57 for 50 mg/m². The MTD was defined at the level of 20 mg/m². As expected from the small patient numbers in each cohort, the confidence intervals around these estimates are wide. The 90% confidence interval for the probability of a DLT at 20 mg/m²/wk was 0.04, 0.36.

### Table 1. Patient Characteristics

| Gender  | Male | Female |
|---------|------|--------|
| Age, years |
| Median   | 63   |
| Range    | 39-78 |

| Karnofsky performance status no. | 100 | 90 | 80 | 70 |
|----------------------------------|-----|----|----|----|
|                                  | 2   | 3  | 10 | 2  |

| Tumor Site no. | oral cavity | oropharynx | larynx | hypopharynx | unknown primary | Maxillary sinus |
|----------------|-------------|-------------|--------|-------------|----------------|----------------|
|                | 6           | 10          | 3      | 3           | 2              | 1              |

### Table 2. Characteristics of Head and Neck Malignancies in 25 Patients

| Tumor Site no. | N0 | N1 | N2 | N3 |
|----------------|----|----|----|----|
| X              | 2  | 2  | 3  | 3  |
| 2              | 2  | 3  | 2  | 3  |
| 3              | 1  | 2  | 4  | 3  |
| 4              | 7  | 1  | 4  | 3  |

### Table 3. Acute and Late Toxicities Associated with Various Doses of Twice-weekly Gemcitabine Delivered during Radiotherapy

| Toxicities | 10 mg/m² (n=6) | 20mg/m² (n=8) | 33mg/m² (n=3) | 50mg/m² (n=4) |
|------------|----------------|---------------|---------------|---------------|
| Acute      | <2 [4]         | <2 [3]        | <2 [3]        | <2 [3]        |
| Lymphologic| 6              | 8             | 2             | 1             |
| Mucosal    | 3              | 3             | 3             | 2             |
| Pharyngeal | 2              | 4             | 7             | 1             |
| Skin       | 4              | 2             | 1             | 7             |
| Larynx     | 6              | 4             | 4             | 1             |
| Late       | 2 [2]          | 2 [2]         | 2 [2]         | 2 [2]         |
| Mucosal    | 6              | 5             | 2             | 1             |
| Pharyngeal | 5              | 1             | 6             | 1             |
| Skin       | 4              | 2             | 7             | 1             |
| Larynx     | 6              | 8             | 3             | 4             |

Values represent number of patients.
Of the 25 patients evaluable for tumor control, 15 (60%) had an initial radiological and clinical complete response, 4 had a partial response, and six had progressive disease. At a median follow-up of 30 months, locoregional control was maintained in 8 patients (32%). Distant metastases developed in 10 of 18 patients who survived at least 6 months; the most common site was the lungs. Median survival time was 20.6 months (95% CI: 14.3, 41.8), and the actuarial 2-year survival rate was 41%. Survival was similar for patients receiving lower (10 or 20 mg/m²) or higher (33 or 50 mg/m²) doses of gemcitabine.

Two patients in the 10-mg/m² cohort underwent biopsies of the residual primary tumor after the first infusion of gemcitabine on day 22. Pathological evaluation showed that in both, the specimens were composed of mostly fibroblasts, with a minority consisting of interspersed tumor cells. We concluded that measurements of gemcitabine metabolites in the specimens taken after 4 weeks of radiation therapy would not provide accurate information on drug accumulation in tumor cells. Therefore, no additional biopsies were performed.

Discussion

In this study, the MTD of gemcitabine delivered twice weekly during the final two weeks of a hyperfractionated RT course was 20 mg/m², representing 25% of the MTD of gemcitabine administered twice weekly in a larger number of cycles without radiotherapy [15,16]. This percentage seems higher than previously reported by our group for once-weekly gemcitabine concurrent with radiotherapy, where the MTD was less than 5% of the MTD of gemcitabine monotherapy [10]. However, this is not likely to represent a clinically meaningful improvement in the therapeutic ratio, as the tolerable gemcitabine doses are still too low. In our previous study, we observed undetectable or only trace levels of intracellular tumor phosphorylated gemcitabine following the administration of 10 mg/m² (before radiotherapy), and low intracellular levels of the active drug following the administration of 50 mg/m² [10]. In the present study, these measurements could not be repeated because at the time of gemcitabine administration, approximately 4 weeks after the onset of radiotherapy, there was only a small amount of tumor cells in the biopsy specimens. Nevertheless, our previous findings suggest that the concentrations of the active drug in tumors would be very low after the administration of 20 mg/m². Although twice-weekly administration likely results in an accumulation of the drug in tumor cells over time, its impact would be restricted with only 5 doses administered over the last 2 weeks of radiotherapy.

The clinical results of this study mirror the limited improvement in the therapeutic ratio. The locoregional tumor-control rate of 32% in the current study is close to that observed in other studies of chemo/radiotherapy for nonresectable head and neck cancer [23,24] but lower than the rate of 60% observed in our previous phase I study of once weekly gemcitabine, which included patients with similarly advanced local/regional disease [8]. In that study, the cohorts receiving 50-300 mg/m² gemcitabine demonstrated measurable tumor cell levels of phosphorylated gemcitabine [8]. It is noteworthy that in both our weekly and bi-weekly concurrent gemcitabine studies, the severe toxicities consisted primarily of mucositis and late dysphagia. This pattern was also reported by others utilizing once-weekly administration of low-dose gemcitabine concurrent with radiotherapy [10,11].

What were the reasons for the failure to translate clinically the improvement in the therapeutic ratio observed in the pre-clinical study of twice-weekly gemcitabine? In the mouse model, the DLTs, defined as lip mucositis and weight loss, analogous to the DLTs observed clinically [12], were similar for gemcitabine 100 mg/kg twice weekly and gemcitabine 800 mg/kg once weekly, concurrent with radiotherapy. While being equi-toxic, the anti-tumor effect in the pre-clinical study was higher in the twice-weekly compared with the once-weekly regimen, as indicated by the significantly smaller tumors at 28 days after therapy. This difference in the therapeutic ratio in the pre-clinical study may not have been sufficient to produce a clinically meaningful impact in patients.

Another approach to improve the therapeutic index was suggested by Mason et al. in a preclinical study of different schedules of gemcitabine concurrent with radiotherapy [25]. They determined that the best ratio of tumor response to jejunal mucosal toxicity was observed when gemcitabine was administered 24 hours before radiotherapy. This was associated with faster post-drug recovery of normal cells than tumor cells, providing a “window of opportunity”. Nevertheless, the gain in the therapeutic ratios was small. Thus, we believe that it is unlikely that modifications in the schedule of concurrent gemcitabine-radiotherapy will substantially facilitate higher effective drug dose delivery.

As mucosal damage has been the major toxicity observed in the current as well as all other trials of gemcitabine-RT, effective mucosal protectors may facilitate the safe delivery of higher concurrent gemcitabine doses. The radiation protector amifostine has been suggested to reduce bowel toxicity during gemcitabine-radiotherapy in patients with pancreatic cancer [26], and may have a potential to improve the therapeutic ratio in patients with HNC. However, thus far there is no compelling evidence that it can effectively reduce mucositis during chemo-RT regimens [27]. Other, new mucosal protectors require a validation of their efficacy [28,29].

Several features have recently emerged as markers of good prognosis in HNC, such as a history of no smoking, or remote smoking, in human papillomavirus (HPV)-related oropharyngeal cancers [30]. However, all the patients who participated in our study had advanced locoregional disease, and most of those with primary oropharyngeal cancers were heavy smokers. Better therapies are required for these patients. Whether or not effective induction chemotherapy may improve the outcome in these poor prognosis patients is not yet clear [31,32]. Recent reports that hypoxic radiosensitizers and hypoxic cytotoxins are most effective in patients with P16-negative tumors (prevalent in high-risk patients), are encouraging avenues to increase local-regional tumor control, and require validation [33]. If such radiosensitizers demonstrate improvement in the therapeutic ratio, it would be feasible to administer them concurrent with RT and with systemic-acting chemotherapy such as cisplatin, which is not likely to be feasible together with gemcitabine using the schedule we described. As long as radiosensitizers lack improved therapeutic ratio, delivering full-dose chemotherapy can only be feasible as induction pre-RT.

At the time this protocol was written and accruing patients, the results of recent randomized studies showing that there was no benefit for altered fractionated RT concurrent with chemotherapy compared with standard fractionated RT concurrent with chemotherapy [34]. These results suggest that altered fractionation need not be employed in studies of radiosensitization.

Dose escalation aiming at hypoxic or hyperperfused tumor subvolumes whose perfusion is not increased shortly after the start of therapy is a route which we have started to investigate in lieu of systemic hypoxic cytotoxins or radiosensitizers. This strategy relies on highly conformal radiotherapy to reduce the extent of both the well-perfused parts of the tumor as well as non-involved tissues irradiated to a high dose, in an effort to improve the therapeutic ratio.
References

[1] Pignon JP, Bourhis J, Domenge C, and Designé L (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355, 985–995.

[2] Pignon JP, Maître AL, Maillard E, and Bourhis J (2009). MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1), 4–14.

[3] Adelstein DJ, Li Y, Adams GL, Wagner Jr H, Kish JA, Ensley JF, Schuller DE, Pignon JP, Maitre AL, Maillard E, and Bourhis J (2009). MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92, 92–98.

[4] Zorat PL, Paccagnella A, Cavaniglia G, Loreqqian L, Gava A, Mione CA, Boldrin F, Marchiori C, Lunghi F, and Fede A, et al (2004). Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: a 10-year follow-up. J Natl Cancer Inst 96, 1714–1717.

[5] Vokes EE, Kies MS, Haraf DJ, Stenson K, Dolan ME, Pelaez–Suhem L, and Witt M, et al (2006). Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 24, 1562–1661.

[6] Wendt TG, Grabenbauer GG, Rödel CM, Thiel HJ, Aydin H, Rohloff R, Wustrow TP, Iro H, Popella C, and Schalhorn A (1998). Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter trial. J Clin Oncol 16, 1318–1324.

[7] Lawrence TS, Eisbruch A, and Shewarch DS (1997). Gemcitabine mediated radiosensitization. Semin Oncol 24(Suppl. 7), 24–28.

[8] Eisbruch A, Shewarch DS, Bradford CR, Littles JF, Teknos TN, Chepeha DB, Marentette LJ, Terrell JE, Hogikyan ND, and Dawson LA, et al (2003). Radiation concurrent with gemcitabine for locally advanced head and neck cancer: a phase I trial and intracellular drug incorporation study. J Clin Oncol 19, 792–799.

[9] Eisbruch A, Lyden T, Bradford CR, Dawson LA, Hazer MJ, Miller AE, Teknos TN, Chepeha DB, Hogikyan ND, and Terrell JE, et al (2002). Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Biol Phys 53, 23–28.

[10] Aguilar-Ponce J, Granados-García M, Villavicencio V, Poivét-Chacón A, Green D, Dueñas-González A, Herrera-Gómez A, Luna-Ortiz K, Alvarado A, and Martínez-Said H, et al (2004). Phase II trial of gemcitabine concurrent with radiation for locally advanced squamous cell carcinoma of the head and neck. Ann Oncol 15, 301–308.

[11] Specenier PM, Weyler J, Van Laer C, Van den Weyngaert D, Van den Brande J, Corry J, Rischin D, Smith JG, D’Costa IA, Hugos PG, Sexton MA, Sizeland A, and Forastiere AA (2003). An Intergroup phase III comparison of standard radiotherapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21, 92–98.

[12] Vokes EE, Kies MS, Haraf DJ, Stenson K, Dolan ME, Pelaez–Suhem L, and Witt M, et al (2006). Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 24, 1562–1661.

[13] Dombernowsky P (1994). Phase II study of gemcitabine (2′-deoxycytidine (gemcitabine). J Clin Oncol 12, 2808–2814.

[14] Brizel DM (2007). Pharmacologic approaches to radiation protection. J Clin Oncol 25, 4804–4809.

[15] Peters L and Rischin D (2012). Elusive goal of targeting tumor hypoxia for chemoradiation therapy in head and neck cancer. Lancet Oncol 13, 145–153.

[16] Pignon JP, Bourhis J, Domenge C, and Designé L (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355, 985–995.

[17] Corry J, Rischin D, Smith JG, D’Costa IA, Hugos PG, Sexton MA, Sizeland A, Lyons B, and Peters LJ (2000). Radiation with concurrent late chemotherapy intensification (‘chemoboost’) for locally advanced head and neck cancer. Radiother Oncol 54, 123–127.

[18] Rischin D, Peters L, Fisher R, Macann A, Denham J, Poulson M, Jackson M, Kenny L, Pennniment M, and Corry J, et al (2005). Tirapazamine, cisplatin, and radiation versus fluorouracil, cisplatin, and radiation in patients with locally advanced head and neck cancer: A randomized phase II trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02). J Clin Oncol 23, 79–87.

[19] Bourhis J, Overgaard J, Audry H, Corry J, Rischin D, Smith JG, D’Costa IA, Hugos PG, Sexton MA, Sizeland A, Lyons B, and Peters LJ (2000). Radiation with concurrent late chemotherapy intensification (‘chemoboost’) for locally advanced head and neck cancer. Radiother Oncol 54, 123–127.

[20] O’Quigley J, Pepe M, and Fisher L (1990). Continual reassessment method: a practical design for phase I clinical trials in cancer. Biometrics 46, 33–48.

[21] Goodman SN, Zahurak ML, and Piantadosi S (1995). Some practical improvements in the continual reassessment method for phase I studies. Stat Med 14, 1194–1161.

[22] Strojan P, Karner K, Slob L, Soba E, Fajdiga J, Jancar B, Anicin A, Budimla M, and Zaloktink B (2008). Concomitant chemoradiotherapy with mitomycin C and cisplatin in advanced unresectable carcinoma of the head and neck: phase II-I clinical study. Int J Radiat Oncol Biol Phys 72(2), 365–372.

[23] Milano MT, Haraf DJ, and Stenson KM (2004). Phase I study of concomitant chemoradiotherapy with paclitaxel, fluorouracil, gemcitabine, and twice-daily radiation in patients with poor-prognosis head and neck cancer. Clin Cancer Res 10, 4922–4926.

[24] Mason KA, Milas L, Hunter NR, Elshaikh M, Buchmiller L, Kishi K, Hittelman K, and Ang KC (1999). Maximizing therapeutic gain with gemcitabine and fractionated radiation. Int J Radiat Oncol Biol Phys 44, 1125–1135.

[25] Phan TP, Crane CH, Janjan NA, Vrdoljak E, Milas L, and Mason KA (2001). WR-2721 reduces intestinal toxicity from concurrent gemcitabine and radiation treatment. Int J Pancreatol 29, 19–27.

[26] Pignon JP, Bourhis J, Domenge C, and Designé L (2000). Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 355, 985–995.

[27] Vokes EE, Kies MS, Haraf DJ, Stenson K, Dolan ME, Pelaez–Suhem L, and Witt M, et al (2006). Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. J Clin Oncol 24, 1562–1661.

[28] Fields MT, Eisbruch A, Normolle D, Orfali A, Davis MA, Pu AT, and Lawrence TS (2000). Radiosensitization produced in vivo by once–vs twice-weekly 2′-deoxy-2′-deoxycytidine (gemcitabine). Int J Radiat Oncol Biol Phys 47, 785–791.

[29] Poplin EA, Corbett T, Flaherty L, Tarassof P, Redman BG, Valdivieso M, and Baker I (1992). Diffiorideoxycytidine (dFdC): Gemcitabine-A phase I study. Invest New Drugs 10, 165–170.

[30] Lund B, Ryberg M, Petersen PM, Anderson H, Thatchet N, and Dombernowsky P (1994). Phase II study of gemcitabine (2′,2′-dideoxyoxycytidine) given as a twice weekly schedule to previously untreated patients with non-small cell lung cancer. Ann Oncol 5, 852–853.

[31] Gordon AS, Glisson BS, Ang KK, Morrison WH, Lippman SM, Byers RM, Garea F, Clayman GL, Shin DM, and Callender DL, et al (1999). Phase I/II trial of radiation with chemotherapy ‘boost’ for advanced squamous cell carcinomas of the head and neck: Toxicities and responses. J Clin Oncol 17, 2390–2395.

[32] Gordon AS, Harris J, Vokes EE, Forastiere AA, Ridge JA, Jones C, Horwitz EM, Glisson BS, Nabell L, and Cooper JS, et al (2004). Preliminary results of Radiation Therapy Oncology Group Protocol 97-03: A randomized phase II trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol 22, 2856–2864.