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Alternating chemotherapy: Gemcitabine and cisplatin with concurrent radiotherapy for treatment of advanced head and neck cancer

J.L. Aguilar-Ponce [a,*], M. Granados-García [b], J.C. Cruz López [e], F. Maldonado-Magos [c], M.A. Alvarez-Avitia [a], O. Arrieta [d], I. González-Ramírez [d], G. Lara-Cruz [b], I. Martinez-Juárez [b], R. Medina-Santillan [f], C. Castillo-Hernández [f], J. De la Garza-Salazar [d]

[a] Department of Medical Oncology, Instituto Nacional de Cancerología, Mexico City, Mexico
[b] Department of Surgery, Instituto Nacional de Cancerología, Mexico City, Mexico
[c] Department of Radiotherapy, Instituto Nacional de Cancerología, Mexico City, Mexico
[d] Department of Basic Investigation, Instituto Nacional de Cancerología, Mexico City, Mexico
[e] Department of Oncology, ISSSTE, Puebla, Mexico
[f] College of Medicine, Instituto Politecnico Nacional, Mexico City, Mexico

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SUMMARY

Background: Many studies have shown gemcitabine and cisplatin are radiosensitizers. Concurrent chemoradiation seems to be an efficient approach for treatment of advanced head and neck cancer (HNC), but toxicity is significant.
Objective: To evaluate safety and explore efficacy of alternating chemotherapy with gemcitabine and cisplatin concurrent with radiotherapy in patients with advanced non-metastatic HNC.
Patients and Methods: Twenty-eight patients diagnosed with advanced Squamous Cell Carcinomas of the Head and Neck (SCCHN) in stages III (28%), IVa (36%), and IVb (36%) were treated with gemcitabine: 100 mg/m^2 alternating with cisplatin: 50 mg/m^2 concurrent with radiotherapy at doses of 2 Gy/day until completing 70 Gy. While awaiting for concurrent treatment, eleven patients received induction chemotherapy with cisplatin: 100 mg/m^2 and 5-FU: 1000 mg/m^2. Toxicity, especially in relation to mucositis, xerostomy, dysphagia, leucopenia and radiodermitis was evaluated.
Results: 5-year progression-free survival was 27.8 ± 17.2% (CI-95: 0–61.5) and overall survival was 55.9 ± 11% (CI: 34.4–77.5). Overall response rate was 93%; complete response was 64.3% and partial response was 28.6%. Extensive surgery for primary site was avoided in 19 patients (70.4%). Grade 3–4 adverse events were mucositis (46.4%), leucopenia (14.2%), dysphagia (25%), xerostomy (10.7%) and radiodermitis (3.6%). Response rates and toxicity were not significantly different among those patients with and without induction chemotherapy, but survival was higher in patients receiving induction.
Conclusions: Gemcitabine alternating with cisplatin concurrent with radiotherapy is an active and safe treatment that deserves further study.

Introduction

According to (MACH-NC) meta-analysis, concurrent chemoradiation is associated with an 6.5% absolute survival benefit when compared with radiotherapy alone in treatment of head and neck carcinomas[1] therefore concurrent chemoradiation is now an standard of treatment for very advanced, unresectable carcinomas and one promising alternative for organ conservation in selected patients with moderately advanced disease.[2,3]

One study compared radiotherapy concurrent with polychemotherapy vs. monotherapy. The study showed patients treated with polychemotherapy had better regional control, organ conservation, and diminished distant recurrence, although toxicity was significant.[4]

Cisplatin is the most used drug for concurrent chemoradiation, but doses and schedules await standardization. Proposed doses vary between 1 and 6 mg/m^2/day; from 10–150 mg/m^2 per week, and for 5-day infusion schedules most used dose is 100 mg/m^2 every 3 weeks. In 2003, 16 studies of concomitant cisplatin and radiotherapy were analyzed; results suggested that fractionated schedules and daily administration produced better results, notwithstanding this was less suitable for clinical practice.[5]

* Corresponding author. Address: Instituto Nacional de Cancerología, San Fernando 22, Col. Sección XVI, Tlalpan 14080, México DF, Mexico. Tel.: +52 56 28 04 00x840.
E-mail address: oncoincan@hotmail.com (J.L. Aguilar-Ponce).

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Five mechanisms have been proposed to explain the radio-sensitizing effects of cisplatin: (1) inhibition of DNA repair mechanisms; (2) sensitization of hypoxic cells; (3) inhibition of the cell cycle; (4) DNA adduct formation, and (5) suppression of tumor - neo-angiogenesis. Possibly, in vivo, all these events diminishes resistance to radiotherapy.[6,7]

Gemcitabine also is employed as radiosensitizer in concomitant schedules with radiotherapy. It is an antimetabolite analog of pyrimidine nucleosides (2′,2′-difluoro-2′deoxycytidine; dFdC). Gemcitabine interferes with DNA synthesis by inhibition of ribonucleotide reductase, causing depletion of the deoxynucleotides required for DNA synthesis. In addition, gemcitabine competes with deoxycitidine triphosphate when incorporated into DNA chains. The radiosensitizing effect is explained by cell cycle arrest, induction of programmed cell death, and sensitizing radio-resistant hypoxic cells. Gemcitabine is retained as a cytotoxic triphosphate with a documented half-life of 72 h.[8–10]

Gemcitabine is easily administered and well tolerated in low doses.[11–13] Eisbruch reported a phase I study, where gemcitabine was well tolerated at doses of 50–300 mg/m^2 and was associated with a significant radiosensitizing effect in squamous cell carcinomas of the head and neck (SCCHN).[14] Raguse and Specenier independently published three additional studies, utilizing concurrent gemcitabine with radiotherapy in an analogous scheme employed by our group. These studies reported complete responses in 68%, 48%, and 61%, respectively; the highest toxicity was grade 3 and 4 mucositis, in 24%, 68%, and 74%, respectively.[8,9]

Synergism between cisplatin and gemcitabine is well-documented.[15–19] Several clinical trials have explored combining gemcitabine and radiotherapy in the treatment of a variety of neoplasms. Clinical studies using gemcitabine as radio sensitizer included tumors where the role of radiotherapy is well established, such as cervical cancer, breast cancer, and others.[20–23] In these studies gemcitabine exhibited cytotoxic activity but also significant toxicity, especially in advanced diseases such as NSCLC.[24–26]

Induction chemotherapy before definitive locoregional treatment is a well-studied approach; a decrease in distant metastases has been observed, but a significant improvement in survival has not been demonstrated. When chemotherapy and radiation are used concomitantly, an improvement in locoregional control can be identified but distant metastases rise as a common cause of treatment failure, suggesting that induction chemotherapy followed by concurrent chemoradiation may improve overall treatment success. Results of some trials using induction chemotherapy and concurrent chemoradiotherapy have been very encouraging.[27–29]

Induction chemotherapy would enhance systemic control meanwhile alternating cisplatin and gemcitabine concurrent with radiotherapy would improve locoregional control by overcoming radio-resistance in patients diagnosed with advanced SCCHN. We retrospectively analyzed our experience with the main objective of evaluating safety and exploring efficacy of this combined scheme.

Materials and methods

Patients diagnosed with local and, or regionally advanced non-metastatic (stage III, IVa, and IVb; AJCC, 2002[30]), biopsy proven squamous cell carcinomas of head and neck, without previous treatment were enrolled. Other criteria included a Karnofsky score > 70%, age > 18 years, and life expectancy > 3 months. We included patients with potentially resectable disease who refused surgery.

Institutional Review Board approved the study. All patients agreed and signed an informed consent. Renal, hepatic, and hematopoietic functions were evaluated. Bilirubin less than 1.5 mg/dl, alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) less than three times the higher normal range, hemoglobin higher than 10 g/dl, white blood cells higher than 4,000 /ml, platelet count higher than 100,000/ml, creatinine less than 1.5 mg/dl, and a 24-h urinary creatinine clearance higher than 60 ml/min were mandatory for inclusion.

Patients with unstable concomitant and systemic diseases as ischemic or hypertensive cardiopathy and diabetes mellitus with significant nephropathies were excluded.

Treatment

Patients received gemcitabine (100 mg/m^2 in 250 ml of saline solution in a 30-min intravenous infusion) on weeks 1, 3, 5, and 7 with antiemetic therapy when necessary, and cisplatin (50 mg/m^2 in 500 ml of saline solution in a 2-h IV infusion) on weeks 2, 4, and 6, preceded by the administration of aprepitant, ondansetron, dexametasone (8 mg IV), and 125 ml of mannitol 20%, prior to and after cisplatin administration.

Radiotherapy was administered 5 days a week, 2 Gy per day until completing 70 Gy; irradiation fields included primary site and neck nodes at risk of microscopic disease. Radiotherapy fields commonly used were two lateral opposite fields and one anterior field on lower neck. Cobalt machine or a linear accelerator of 6 MV was used. Radiation to spinal cord was restricted to 45 Gy, and 54 Gy to brain stem and optical nerves, respectively.

While awaiting concurrent treatment with radiotherapy, eleven patients received induction chemotherapy with cisplatin: 100 mg/m^2 on day 1, and 5-FU: 1000 mg/m^2, on days 1–4, every 3 weeks, for 2 planned cycles.

Surgery was attempted after partial response in primary site or neck nodes, if appropriate, and as a complementary neck dissection when the original size of neck nodes was >3 cm, even if they reached a complete response.

Assessment

Efficacy

Baseline and subsequent tumor evaluation was done by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), and endoscopic studies when indicated. Tumor response was defined according to modified World Health Organization (WHO) criteria. Tumor responses were defined as follows: complete response, complete disappearance of all lesions; partial response, *a* >50% reduction in size of index lesions compared with baseline and no evidence of progression (at least for 30 days), and progressive disease, *a* > 25% increase in size of index lesions or the appearance of one or more new lesions. A separate evaluation of regional (neck) disease was performed to describe and clarify responses. Definitive overall tumor response was assessed on days 42–56 after conclusion of the study regimen.

Safety

Patients were evaluated on weekly basis during treatment in order to monitor toxicity. In the case grade 4 toxicity, treatment was suspended temporarily until toxicity subsided to safe levels. Adverse effects were recorded according to National Cancer Institute (NCI) Toxicity Criteria (version 3).

Statistical analysis

We used the SPSS software package (v.14) to perform the statistical analysis. Continuous variables were summarized as arithmetical means and standard deviations (errors), and categorical