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Safety and Efficacy of Concurrent Cisplatin and Radiotherapy in Inoperable or Metastatic Squamous Cell Esophageal Cancer

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Acta Oncologica Vol. 41, No. 5, pp. 457–462, 2002

Between August 1996 and May 1999, 50 consecutive, previously untreated patients with carcinoma of the esophagus and who were inoperable for various reasons were treated with weekly doses of cisplatin (35 mg/m^2, maximum 7 cycles) concurrent with either 66 Gy/33 fractions external beam radiotherapy (EBRT) (n = 42) or 50 Gy/25 fractions EBRT and two insertions of high-dose-rate intraluminal radiotherapy of 6 Gy each, spaced a week apart (n = 8). Eighty-two percent (41/50) of the patients received the stipulated radiotherapy (RT) dose. Seventy-six percent (38/50) received at least 6 cycles of chemotherapy. Neutropenia in the form of WHO grade II-12% (6/50) and grade III-2% (1/50) was observed. Grade III emesis was seen in 8% (4/50). Improvement in the swallowing status was seen in 84% (42/50). Median duration of dysphagia relief was 6 months. The median overall survival was 9 months with 17% estimated to be alive after 4 years. Combined treatment with single agent cisplatin and definitive radiotherapy for inoperable cancer of the esophagus is safe, well tolerated and reasonably efficacious.

Received 1 November 2001
Accepted 14 June 2002

One of the strategies used to improve on the dismal survival statistics of cancer of the esophagus is concurrently to combine chemotherapy with radiotherapy. The Intergroup trial has demonstrated that concurrent therapy with cisplatin (CDDP) and 5-fluorouracil (5-FU) along with radiotherapy is superior to radiotherapy alone, as measured by improved local control and survival rates for cancer of the esophagus (1). This trial also documented severe or life-threatening toxicity in 44% and 20% of cases, respectively, and overall compliance to the stipulated protocol was about 54%. A similar but less dose-intensive regimen in a phase III trial using CDDP and 5-FU could not replicate these results, and furthermore, was associated with significantly higher levels of toxicity than those found in the radiotherapy arm (2). The present study is a report on the safety and efficacy of a moderately intensive chemotherapy schedule of single agent CDDP given concurrently with radiotherapy in inoperable or metastatic esophageal cancers.

MATERIAL AND METHODS

Between August 1996 and May 1999, fifty previously untreated, consecutive patients were enrolled in this study. These patients were referred to the Department of Radiotherapy from the Surgical and Medical Departments of Gastroenterology at this institute following an initial evaluation which, in the opinion of the surgeon, rendered them inoperable for various reasons. All patients gave written informed consent.

Inclusion criteria

Patients were included if they had a Karnofsky performance status (KPS) of ≥ 60, a hemoglobin count of ≥ 10 g%, total leucocyte counts $\geq 4 \times 10^3/\text{mm}^3$, platelet counts $\geq 10^5/\text{mm}^3$, serum creatinine ≤ 1.6 mg%, blood urea nitrogen < 22 mg%, total bilirubin < 1 mg%, SGPT ≥ 40 U/L and SGOT 40 U/L. Patients with adenocarcinoma, a second primary neoplasm or a recurrent disease were excluded from this study. Those with non-regional nodal

 ISSN 0284-186X

metastasis or spread to liver/lung were not excluded if they satisfied the other criteria of eligibiligy.

Staging workup

Following a history and physical examination, patients underwent an endoscopic evaluation and biopsy of the disease. A barium contrast evaluation and a CAT scan evaluation of the thorax and upper abdomen (including liver and suprarenal areas) were performed to further evaluate the disease extension and spread. Complete hemograms, liver function tests and renal function tests and a chest x-ray PA view were done in all patients. In addition, if clinically indicated, patients also underwent a radionuclide bone scan. Tumor stages were defined as follows, with modifications as suggested by Herskovic et al. (1): T1 tumor involves ≤ 5 cm of esophageal length, with no esophageal obstruction, incomplete circumferential involvement, and no evidence of spread beyond the esophagus; T2 tumor is > 5 cm in length or complete circumferential involvement is evident, and there is no evidence of extension outside the esophagus; and T3 is any of the above with extension outside the esophagus. Node stages were defined as N0 no evidence of regional nodes on CT scan and N1 with mediastinal nodes on CT scan.

Interventions

Radiotherapy

External beam radiotherapy (EBRT) was delivered by mega voltage radiation (telecobalt or 6/10 MV photons) with a minimum source-to-axis distance of 80 cm. The first phase of treatment delivered 36 Gy in 18 fractions, 5 days per week to the radiographically identified tumor with a 5-cm cranio-caudal margin and a 3-cm radial margin. Phase two of the treatment was delivered to the tumor as defined above, with a 2-cm cranio-caudal, medio-lateral and antero-posterior margin by two or three fields as appropriate to a total dose of 66 Gy in 33 fractions. Lung inhomogeneity corrections were routinely performed and the dose prescribed to the isodose which encompassed the planning target volume, usually at 95%. The spinal cord doses were kept below 45 Gy. However, 8 patients received intraluminal radiotherapy (ILRT) after 50 Gy EBRT. Two fractions of 6 Gy at high dose rate (HDR) were given at weekly intervals two weeks after completion of EBRT. The dose was prescribed to the radiographically identified tumor with a 2-cm cranio-caudal margin at 5 mm from the surface of the applicator, which was 6, 8 or 10 mm in diameter (Ralstron 20B, Shimadzu, Japan) or 6 mm in diameter (Microselectron HDR, Nucletron, The Netherlands). The decision to use brachytherapy was individualized at the discretion of the physician delivering the treatment. The extrapolated response dose for tumor (ERDt) was used as a surrogate variable for total dose as 8 patients had HDR-ILRT following EBRT and a straightforward addition of the two was not possible. ERDt was done using the following equation (3)

$$\mathrm{ERDt} = \mathrm{D}\left(1 + \frac{\mathrm{d}}{\alpha/\beta}\right) - \frac{0.693}{\alpha} \times \frac{\mathrm{t}}{\mathrm{tpot}}$$

where D is the total dose of EBRT or HDR-ILRT, d is the dose per fraction, α/β is taken as the tumor characteristic with a value of 6 Gy (4), α is taken as 0.3, t is the overall treatment time in days and tpot is the median potential doubling time taken as 6.8 days (5).

Chemotherapy

Following prehydration and antiemetic administration, CDDP was given as a short (30-min) infusion in a dose of 35 mg/m^2 (maximum 50 mg) weekly for 7 cycles along with mannitol diuresis and post-chemotherapy hydration, generally as an outpatient procedure. Radiotherapy was given on the same day as chemotherapy, after 30 min. Chemotherapy was postponed by one week to allow for hematological recovery if the total leucocyte count was less than 3500/mm^3.

Response assessment and follow-up

Evaluation after treatment consisted of physical examination and a barium esophagography once a month for the first year and every 3 months for the second and subsequent years, or earlier if clinically indicated. Esophagoscopy and biopsy were done to determine the cause of recurring or persisting dysphagia, but this was infrequent as the use of these invasive procedures was avoided in patients with poor performance status. Dysphagia scores were recorded pre- and post-treatment and also at every follow-up. Based on these scores, dysphagia relief was scored as improved, unchanged or worsened. Patients were scored as dysphagia free only if solids or soft solids could be consumed without appreciable difficulty during or after treatment. Those not able to do so were scored as failures from the first day of treatment. Dysphagia-free interval (DFI) and overall survival (OS) were computed from the day of initiation of treatment. Dysphagia-free status was terminated when the patients reported any sustained inability to swallow solids or soft solids despite repeated attempts at dilatation when feasible.

Acute and late toxicities

The various drug-related toxicities were documented weekly during the treatment using the RTOG/EORTC criteria for acute toxicity (6).

Statistical analysis

Estimates of DFI and OS were done using the Kaplan–Meier method and univariate comparisons were made using the log-rank statistic. Multivariate analysis of factors affecting these endpoints was performed using the Cox's proportional hazards model. The factors evaluated were: age,

gender, KPS, weight loss, pretreatment hemoglobin, (pretreatment) dysphagia duration, dysphagia grade, site of disease, length of disease, endoscopic features, T stage, N stage, M stage and ERDt. Patients alive or controlled at the time of reporting were considered censored observations. Death due to any cause was considered an event for both DFI and OS.

RESULTS

The characteristics of the patients and their tumors are shown in Tables 1 and 2. Of the 7 patients with metastasis at diagnosis, 6 had non-regional nodal metastasis (2 supraclavicular and 4 in the celiac and/or para-aortic region), while the remaining patient had a spread to the skeletal system and liver.

Compliance to interventions and toxicity

Compliance to interventions is presented in Table 3. Nine patients received less than 66 Gy for the following reasons. The condition of 6 patients deteriorated on treatment as 3 of them had distant metastases at diagnosis, 1 patient developed pulmonary tuberculosis, 1 had hematemesis and 1 had personality problems associated with alcoholism. Additionally, 2 patients could not tolerate the interventions and 1 refused ILRT. Of the 12 patients who received fewer than 5 cycles of chemotherapy, 9 of these were due to reasons stated previously with regard to poor compliance to the radiotherapy schedule. In addition, 2 patients had severe emesis due to chemotherapy and 1 had grade 2 leucopenia and hence received fewer than the stipulated cycles. As Table 4 shows, grade 3 leucopenia was seen in only 1 patient and grade 3 emesis in 4 patients. Exact protocol compliance was seen in 76% (38/50).

Table 1

Characteristics of patients

Characteristic		Number (%)
Age (years)		
Median, range	60, 30–86	
Gender		
Male		32 (64)
Female		18 (36)
Karnofsky performance scale		
60		2 (4)
70		12 (24)
80		20 (40)
90		16 (32)
Weight loss (%)		
Median, range	12.5, 0–33	
No data		9 (18)
Hemoglobin (g%)		
Median, range	11.9, 9–15	
Dysphagia duration (months)		
Median, range	3, 1–30	
Dysphagia grade		
Nil		1 (2)
To solids		20 (40)
To soft solids		21 (42)
To liquids		6 (12)
Absolute		2 (4)

Table 2

Tumor characteristics

Characteristic		Number (%)
Site		
Upper		5 (10)
Mid		26 (52)
Lower		19 (38)
Length (cm)		
Median, range	7, 3–14	
Endoscopic features		
Proliferative		28 (56)
Ulcerative-infiltrative		12 (24)
Stricture		9 (18)
Unknown		1 (2)
T stage		
T1		2 (4)
T2		31 (62)
T3		17 (34)
N stage		
N0		31 (62)
N1		19 (38)
M stage		
M0		43 (86)
M1		7 (14)

Response to treatment, and patterns of failure

The median follow-up of all surviving patients was 9 months with a range of 12 to 48 months and as of this reporting,

Table 3

Compliance to interventions

Variable		Number (%)
EBRT dose		
$\leq$50 Gy		2 (4)
51–65 Gy		7 (14)
66 Gy		33 (66)
50 Gy (+ILRT 6 Gy × 2)		8 (16)
Radiotherapy duration (days)		
Median, range	52, 14–113	
ERDt (Gy 6)		
Median, range	69.2, 22.7–74.7	
Chemotherapy cycles		
1–3		5 (10)
4–5		7 (14)
6–7		38 (76)

Abbreviations: EBRT = external beam radiotherapy; ILRT = intraluminal radiotherapy; ERDt = extrapolated response dose for tumor.

Table 4

Chemotherapy toxicity

Toxicity	Number (%)
Anemia (g/dl)	
Grade 0 (> 11)	21 (42)
Grade I (9.5–10.9)	19 (38)
Grade II (8–9.4)	10 (20)
Leucopenia ($\times 10^3/mm^3$)	
Grade 0 (> 4)	39 (78)
Grade I (3.0–3.9)	4 (8)
Grade II (2.0–2.9)	6 (12)
Grade III (1.0–1.9)	1 (2)
Emesis	
Grade 0 (none)	29 (58)
Grade I (nausea)	6 (12)
Grade II (transient vomiting)	11 (22)
Grade III (vomiting requiring therapy)	4 (8)

9 patients are still alive. In terms of dysphagia relief, there was an improvement in the swallowing status of 84% (42/50) of patients compared to their pretreatment status, while in the remaining 16% (8/50), there was no change. Only 3 patients in this entire group of 50 had pretreatment dilatation of the esophageal growth and of these patients, 2 were stented. The median duration of dysphagia relief was 6 months for all patients (Fig. 1) with a 17% probability of remaining dysphagia free at 4 years. Similarly, the median overall survival for all patients was 9 months (Fig. 2) with a 17% survival probability at 4 years. In a subset analysis of non-metastatic patients (n = 43, figures not shown), the median dysphagia-free duration was 7 months while the median OS was unchanged at 9 months with a 4-year survival probability of 20%.

One patient who developed a tracheo-esophageal fistula (TEF) during attempted dilatation prior to initiation of radiotherapy was stented and treatment was continued. A further two patients developed TEF during treatment and 2 during the follow-up period. Forty-two percent (21/50) had strictures and a biopsy proof of disease could be obtained in 5 of these patients, although most of the strictures appeared to be associated with disease as revealed by barium esophagogram or endoscopy.

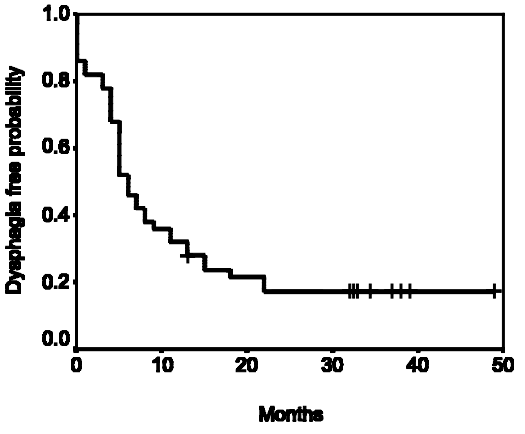

Fig. 1. Dysphagia-free interval.

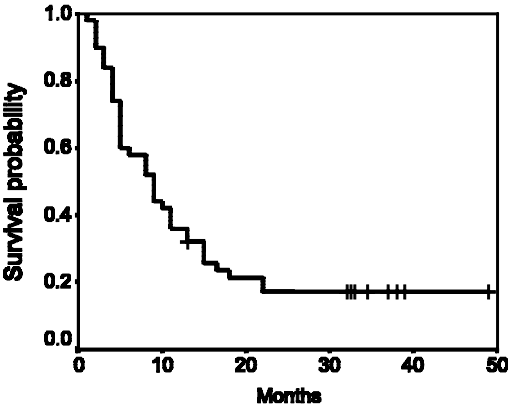

Fig. 2. Overall survival.

The patterns and sites of failure are shown in Table 5. Local recurrence/persistence as any component of failure was seen in 52% (26/50) of patients. Twelve percent (6/50) had distant failure alone and an additional 8% (4/50) failed both locally and at distant sites. The sites of distant failure were: liver, 5; bone, 2; ascites, 4; brain, 1 and non-regional nodes, 3 (para-aortic nodes, 2 and neck nodes, 1). (The numbers do not add up to 10 because some patients had more than one site of failure.) The cause of death could not be ascertained in 18% of patients (9/50) in whom death was intimated to us through postal correspondence. Eighteen percent of patients (9/50) were alive at the time of analysis.

A univariate analysis of factors influencing DFI and OS was undertaken. Absence of metastasis (log-rank $p = 0.03$ for DFI, $p = 0.05$ for OS) and ERDt > 60 Gy 6 (log-rank $p = 0.02$ for DFI, $p = 0.01$ for OS) were found to be favorable factors for DFI and OS. In the multivariate model, while the absence of metastasis was retained as a factor of significance for DFI, dysphagia duration was introduced as a factor of independent prognostic significance for DFI and OS.

Table 5

Patterns of failure

Site of failure	Number (%)	
Local	19 (38)	
Persistence		11
Recurrence		8
Distant failure alone	3 (6)	
Local + distant failure	3 (6)	
Distant metastasis at diagnosis	7 (14)	
Local failure		3
Local + distant		1
Distant		3
Alive and NED	9 (18)	
Unknown causes of death	9 (18)	

DISCUSSION

The primary aim of this analysis was to determine the safety profile and efficacy of single agent CDDP used concurrently with RT in inoperable and metastatic esophageal carcinoma.

Toxicity profiles can be a function of both radiotherapy (RT) dose/fractionation, treated volume and chemotherapy (CT) schedules. Broadly, concurrent CT regimes have consisted of 5-FU as a single agent, 5-FU + CDDP, 5-FU + mitomycin-C (MMC); and CDDP + etoposide (VP-16) combinations. When single agent 5-FU was used as a continuous infusion (CI) for 6–7 weeks at 250–300 mg/m^2 for 5 days in a week, diarrhea was a prominent symptom for 14% of the patients while grade 3 hematological toxicity was seen in 4% of the patients with an overall compliance of 89% (7). 5-FU in 2 cycles of 20 mg/kg/day as a CI over 4 days and spaced 6 weeks apart with MMC 8 mg/m^2 on day 1 of the first cycle when given concurrently with split-course RT of 50–55 Gy over 8 weeks resulted in a 100% compliance and no grade 3 hematological toxicity (8). However, a similar CT schedule concurrent with 40–60 Gy RT resulted in an overall compliance of 65% and grade 4 hematological toxicity in 3% of patients in a phase III trial (9). This difference in compliance was probably due to the use of split-course RT in the previously mentioned study. Two cycles of 5-FU (1 g/m^2/day for 4 days) + CDDP (70 mg/m^2 day 1) given concurrently with 40 Gy of split-course RT resulted in a high compliance of 89% and grade 3 hematological toxicity in 3% patients (10).

The Intergroup randomized trial had used 2 cycles of concurrent and 2 cycles of adjuvant CDDP + 5-FU (5-FU 1 g/m^2/day CI × 4 days and CDDP 75 mg/m^2 day 1 of each course) concurrently with 50 Gy EBRT. This resulted in a compliance of 54%, with grade 3 hematological toxicity in 44%, grade 4 in 20% and death in 2% of patients (1). The above CT schedule (with modifications) when given as 3 cycles of neo-adjuvant treatment, followed by 2 cycles given concurrently with 64.8 Gy EBRT resulted in a similar compliance of 66% but increased hematological toxicity (grade 3, 39%; grade 4, 23%) and death rates (11%) (11). Concurrent CDDP + VP-16 given in a neo-adjuvant, concurrent and adjuvant protocol with 50–55 Gy RT resulted in grade III/IV hematological toxicity in 53% of patients in another report (12). The low frequency of grade 3 hematological toxicity (2%), of grade 3 emesis (8%) and a compliance to protocol of 76% is not surprising as only single agent CDDP was administered weekly with 66 Gy EBRT or 50 Gy EBRT + 6 Gy × 2 HDR-ILRT.

The addition of CT to RT can be expected to potentiate the effect of RT locally and also decrease the incidence of distant metastasis by its systemic effects. This is evident from a review of the patterns of failure in esophageal cancers where the use of chemotherapy resulted in a decrease in the incidence of local failure from 25%–84% to 15%–39% and the incidence of distant failure from 23%–65% to 6%–25% (13). Two prospective single arm studies and one randomized trial using concurrent chemoradiation have shown a reduction in local failure but an increase in distant failure with the addition of CT to RT, thereby suggesting an alteration in the failure patterns from local failure to one dominated by distant metastasis (8, 14, 15). However, the Intergroup trial using 2 cycles of concurrent and 2 cycles of adjuvant 5-FU + CDDP demonstrated a 46% vs. 68% local failure for the CT + RT and RT group, respectively, and a distant metastatic rate of 16% vs. 30%, respectively, which was highly significant and translated into a significant survival gain (1). The current study documented local recurrence/persistence as any component of failure in 52% and distant failure in 20% (12% if patients with distant metastasis at diagnosis are excluded, Table 5)—however, a large number of patients (18%) in whom the cause of death could not be ascertained does not allow a conclusion on the efficacy of this CT + RT protocol in terms of this endpoint.

Dysphagia relief has been studied and stated infrequently in the published literature and it has varied between 59% and 77% in some phase II trials (10, 14, 16). The Intergroup trial stated proportions of patients who had an 'improvement in the ability to swallow' as being 66% for the RT arm and 58% for the CT + RT arm (1). DFI is often not computed in many reported trials and one reason for this could be the degree of subjectivity associated with this interpretation and hence it being a relatively soft endpoint by which to measure efficacy. The current protocol documented 84% patients as having an improvement in their swallowing compared to the pretreatment status with a median duration of dysphagia relief of 6 months and a 17% probability of remaining dysphagia free at 4 years.

Median survival reported in phase I/II concurrent chemo-radiation trials has been relatively encouraging at 11 to 24 months (17, 18). The large variability is most likely influenced by patient selection. For instance, using 2 cycles of 5-FU and MMC concurrently with 40–50 Gy RT, a median of 13 months was reported by Chan et al. (8). However, a similar schedule of CT and 60 Gy of RT in a select early stage 'curative group' resulted in an 18-month median OS and a 5-year survival of 18%, highlighting the importance of patient selection (14). Similarly, using CDDP + VP-16 concurrently with 50–55Gy RT in a group of Stage III and IV patients, a modest median survival of 9.2 months was achieved (12). The Intergroup trial documented a median OS of 14.1 months and a 5-year survival rate of 26% in the CT + RT arm (19). Attempts to be more dose intensive in terms of both CT and RT did not result in additional survival advantage with a 5-year OS of 20% (20). The influence of patient selection on outcome is perhaps best demonstrated in a

randomized study from South Africa in which only patients with T3N0-1 stage disease were accrued and were randomized to receive either 2 cycles of CI 5-FU + CDDP and 40 Gy/10 fractions split-course RT or RT alone. The median OS was 5.6 vs. 4.8 months in the CT + RT and RT groups, respectively (non-significant) (2). The median OS in our analysis was 9 months with a survival probability of 17% at 4 years, which was reasonable considering the locally advanced and inoperable status of these patients and 14% with distant metastasis at diagnosis.

In conclusion, it appears that clinical trials have shown the efficacy of concurrent CT + RT in terms of achieving a longer median and overall survival in carcinoma of the esophagus along with a reduction in local and distant failure rates compared to RT alone But this has generally been at the cost of higher CT-related toxicity, especially with combination CT. However, this study has documented that single agent CDDP chemo-radiotherapy as used in this investigation is safe, well tolerated and reasonably efficacious and warrants comparison with RT alone.

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