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A comparative study of cisplatin-based definitive chemo-radiation in non-metastatic squamous cell carcinoma of the esophagus

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Abstract

Introduction: Esophageal cancer is the seventh most frequent malignancy in Iranian men and the fourth most common cancer in Iranian women. It is also among the 10 most frequent cancers in the world. Definitive chemo-radiation using cisplatin with 5-fluorouracil (5-FU) is known as the standard of care among various chemotherapy regimens used with esophageal cancer patients who are not eligible for surgery. Cisplatin with paclitaxel and cisplatin with irinotecan also have been used often during the past five years. The aim of this research was to compare overall survival (OS) and hematological toxicity rates between these regimens.

Methods: This single-institutional study included 55 patients who were treated with definitive chemo-radiation in the radiation-oncology ward at Shohada-e-Tajrish Hospital in Tehran, Iran, between 2006 and 2013. They received one of four regimens, i.e., cisplatin, cisplatin with 5-FU (old chemotherapy regimens), cisplatin with paclitaxel, or cisplatin with irinotecan (new chemotherapy regimens) as part of their definitive chemo-radiation with curative intent. The Kaplan-Meier estimator was used to estimate the overall survival times, which were compared by using the Breslow test.

Results: The follow-up period was between 26-109 months, with a median of 72 months. OS was not different between the old and new chemotherapy regimen groups ($p = 0.18$). Hematological toxicity (leucopenia) in the old chemotherapy regimen groups (10%) was significantly lower than in the new chemotherapy regimen groups (43%, $p = 0.012$). But OS in cisplatin or cisplatin with 5-FU scheme was statistically better than with the cisplatin with paclitaxel scheme ($p = 0.026$, $p = 0.028$, respectively).

Conclusion: This study showed that OS are similar in both the old and new chemotherapy treatment regimens in esophageal cancer patients who were treated with definitive chemo-radiation. The new chemotherapy treatment regimens should be used with caution as an alternative treatment of cisplatin with 5-FU for further evaluation.

Keywords: Esophageal cancer, Cisplatin, 5-FU, Paclitaxel, Irinotecan, Definitive chemoradiation

1. Introduction

Esophageal cancer is a deadly disease, and it was the seventh leading cause of death due to cancer in the United States in 2012. Also, it is among the 10 most frequent cancers in the world, with an incidence rate exceeding 300,000 new cases annually (1). Most cases of esophageal cancer occur predominantly in developing countries, and they involve squamous cell histology with significant geographical dispersion of the incidence rate (2). In some

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areas, the incidence of esophageal cancer is significantly higher than in others. It seems that in China, India, Japan, and Iran, which are located in the belt of esophageal cancer, there is a higher incidence of this deadly disease (3-4). Now being challenged with patients with esophageal cancer is one of the biggest problems facing oncologists. Although esophageal cancer is a curable disease in its early stages, it often is fatal in the middle and advanced stages. Clinical response to treatment depends on the local and metastatic spread of the disease before treatment (5). Standard treatment in the distant past was surgery, but due to the high rate of recurrence, even in patients with earlier stage cancer, researchers are exploring multi-modality treatment for this group of patients. Concurrent chemo-radiation as neo-adjuvant therapy before surgery, as adjuvant therapy after surgery, and as definitive chemo-radiation has been studied extensively for use in treating esophageal cancer (6-9). The radiation therapy oncology group's (RTOG's) 85-01 trial showed that, in non-metastatic esophageal cancer patients not receiving surgery, definitive chemo-radiation with cisplatin and 5-fluorouracil (5-FU) improved 5-year survival up to 26% compared with patients receiving only radiotherapy (10). Several randomized clinical studies have been conducted on various aspects of using chemo-radiation for esophageal cancer. Cisplatin and 5-FU have been included in the most formal protocols. They have been used in combination with radiotherapy over the last 20 years (11). But a new generation of drugs, such as paclitaxel and irinotecan, is being used in combination with radiotherapy in recent years. Recent efforts with paclitaxel in the treatment of locally-advanced esophageal cancer have shown significant activity, with response rates exceeding 50% (12-14). This study aimed to compare the differences in survival and hematologic toxicity rates between the old generation regimens (cisplatin with or without 5-FU) and the new generation regimens (cisplatin with paclitaxel or cisplatin with irinotecan) in patients with non-metastatic esophageal squamous cell carcinoma (SCC) treated with definitive chemo-radiation.

2. Material and Methods

2.1 Research Design and eligibility criteria

This was single-institutional retrospective-analytical study. The medical records of 235 esophageal cancer patients were investigated for information such as age, gender, body surface area (BSA), pretreatment dysphasia, tumor location in the esophagus, TNM stage, pathology of tumor, chemotherapy protocol type and number, radiotherapy dose, date of diagnosis, and the date of death. Patients who were diagnosed with pathologically localized SCC of the esophagus from stage T1N0-N2M0 to stage T4N0-N2M0 with esophageal cancer were assessed. Clinical TNM staging was defined by endoscopic ultrasonography (EUS) and computed tomography (CT) scans of the neck, chest, and abdomen. All patients were treated with definitive chemo-radiation in the radiation-oncology ward at Shohada-e-Tajrish Hospital in Tehran, Iran, between 2006 and 2013. We studied 55 esophageal cancer patients who met the inclusion criteria at our center from 2006 to 2013. The inclusion criteria were that the patients had a histopathology diagnosis of SCC of the esophagus without distant metastasis and also were treated by definitive chemo-radiation at our center. Patients were excluded from the study if they were without a histopathology diagnosis other than SCC, if they had been treated by esophagectomy, if they presented with distant metastasis, and if they had undergone neo-adjuvant or adjuvant treatments, such as radiation therapy or chemotherapy initiated by another radiation oncology center and if they were without follow-up.

2.2. Data collection

All 55 patients had been treated previously with a linear accelerator (Linac) 9 MV or Cobalt 60 with 30-55 Gray (Gy) in 15-32 fractions. Radiation therapy was used five days per week from Saturday to Wednesday (with the exception of public holidays) with 1.8 Gy or 2 Gy per fraction with 2-dimensional (2D) or 3D treatment planning. Treatment planning was conducted after direct simulation, based on diagnostic images with barium swallow contrast or 3D treatment planning CT images with oral contrast to facilitate localization of the primary site of the tumor. After simulation, in 2D treatment planning, margins from the gross tumor volume (GTV) with a 5-cm margin in the caudal/cranial direction and a 2-cm margin in transversal plane were used to generate the planning target volume (PTV). In 3D treatment planning, the clinical target volume (CTV) was obtained by adding a 3-cm margin in cranial–caudal direction and a 1-cm margin in the transversal plane. Forty-one patients had previously received cisplatin 75-100 mg/m^2 (day 1) with or without 5-FU 750-1000 mg/m^2 (days 1–4) at weeks 1 and 5 during RT with two additional courses in weeks 8 and 11 (RTOG 85-01 protocol). Seven patients previously had received cisplatin 75 mg/m^2 weekly on day 1 with paclitaxel 60 mg/m^2 weekly on days 1, 8, 14, and 22 during radiation therapy, and 7 patients previously had received cisplatin 30 mg/m^2 weekly on days 1, 8, 22, and 29 with irinotecan 65 mg/m^2 weekly on days 1, 8, 22, and 29 during radiation therapy. Hematologic toxicity (only leucopenia) was defined with white blood cells (WBC) < 3000 cells per microliter during chemo-radiation. The 3-year overall survival (OS) rate, 5-year OS rate, and median survival were calculated from the date of diagnosis until the date of death.

2.3. Ethical consideration

The ethical regulations dictated in the act provided by the Research Center of Shohada-e-Tajrish Hospital at Shahid Beheshti University of Medical Sciences (reference number of research ethics committee:4029) were strictly observed. The data were preserved anonymously.

2.4. Statistical analyses

The Kaplan-Meier estimator was used to estimate the overall survival times, and they were compared using the Breslow test. The Cox regression analysis of factors potentially related to overall survival was used to identify the independent factors that might jointly have had a significant effect on overall survival. Fisher's exact test was used to compare the incidence of leucopenia between the two regimens. A p-value < 0.05 (2-sided test) was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences, Version 16 (SPSS, Inc., Chicago, IL, USA).

3. Results

The study included 55 patients, 28 of whom were males (51%) and 27 of whom were females (49%). The median age was 67 (range: 48-87). The follow-up duration was between 26 and 109 months with a median of 72 months. The median BSA was 1.5 m2 (range: 1.25-1.8 m2). Eleven patients (20%) had baseline dysphasia with grade I, 35 patients (64%) had baseline dysphasia with grade II, and 9 patients (16%) had baseline dysphasia with grade III. The location of the tumor in the upper esophagus 14 patients (25%), in the middle esophagus 25 patients (46%), in the lower esophagus 9 patients (16%), and unknown in 7 patients (13%). Clinical T stages were 14.5% T1, 7.3% T2, 65.5%T3, and 12.7% T4 cases. All 55 patients were treated by definitive cisplatin-based chemo-radiation. The median number of treatments of chemotherapy was five courses (range: 1-14 courses). The median cumulative esophageal dose in our series was 50 Gy (range: 35-55 Gy). Twenty-eight patients (51%) received cisplatin chemotherapy simultaneous with definitive EBRT, 13 patients (23.6%) received cisplatin and 5-Fu chemotherapy simultaneous with definitive EBRT, 7 patients (12.7%) received cisplatin and irinotecan chemotherapy simultaneous with definitive EBRT, and 7 patients (12.7%) received cisplatin and paclitaxel chemotherapy simultaneous with definitive EBRT. Forty-one patients (74.6%) were treated with old chemotherapy regimens (cisplatin or cisplatin and 5-FU), and 14 patients (25.4%) were treated with the new chemotherapy regimen (cisplatin and paclitaxel or cisplatin and irinotecan). The patients' and treatment characteristics are shown in Table 1.

Table 1. Patients and treatment characteristics of 55 patients with SCC of esophagus who were treated with chemo-radiation

Characteristics	Median (Range)	Characteristics		n (%)
Age (years)	65 (32-82)	Gender	Female	27 (49)
			Male	28 (51)
BSA[a] (m^2)	1.5 (1.25-1.83)	Baseline Dysphasia	Grade I	11 (20)
			Grade II	35 (64)
			Grade III	9 (16)
Radiotherapy dose (Gy)	50 (30-55)	Tumor Location	Upper Esophagus	14 (25)
			Middle Esophagus	25 (46)
			Lower Esophagus	9 (16)
			Unknown	7 (13)
Treatment course of chemotherapy (number)	5 (1-14)	Treatment Regimen	Cis[b]	28 (51)
			Cis with 5FU[c]	13 (23.6)
			Cis with Irinotecan	7 (12.7)
			Cis with Paclitaxel	7 (12.7)
			Old regimen	41 (74.6)
			New regimen	14 (25.4)
Follow-up Time (months)	72 (26-109)	Clinical tumor Stage	T1	8 (14.5)
			T2	4 (7.3)
			T3	36 (65.5)
			T4	7 (12.7)

[a]BSA: body surface area; [b]Cis:cisplatin; [c]5-FU: 5-fluorouracil

Age, gender, BSA, tumor location, clinical T stage, and the distribution of radiation dose did not differ among the groups. There was no significant relationship between the independent factors (gender, age, BSA, tumor location, and the distribution of radiation dose) in our study and overall survival according to Cox Regression analysis. There was no multicollinearity among the independent variables. The median survival time was 17 months (95% CI = 12.6 - 21.3) in patients who were treated with cisplatin chemo-radiation, 22 months (95% CI = 5.6 - 38.3) for cisplatin with 5-Fu chemo-radiation, 27 months (95% CI = 0 - 68) for cisplatin with irinotecan chemo-radiation, and 5 months (95% CI = 2.4 - 7.5) for cisplatin with paclitaxel chemo-radiation. The median overall survival time was 14 months (95% CI = 8 - 19.9), and it was 17 months (95% CI = 11.8 - 22.1) in patients who were treated with the old chemotherapy regimen, and it was 6 months (95% CI = 4.1 - 7.8) in patients who were treated with the new chemotherapy regimen. Kaplan–Meier survivals estimation of the overall survival for definitive chemo-radiation with cisplatin, cisplatin+5-FU, cisplatin+irinotecan, and cisplatin+paclitaxel are shown in Figure 1 and for definitive chemo-radiation with old regimens and new regimens are shown in Figure 2.

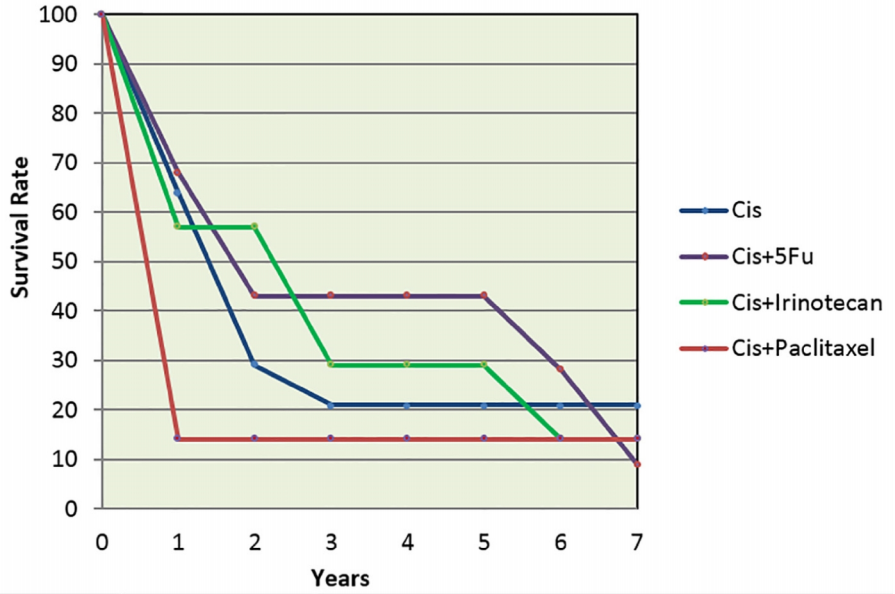

Figure 1. Kaplan–Meier survivals estimation of the overall survival for definitive chemo-radiation with Cisplatin, Cisplatin+5Fu, Cisplatin+Irinotecan and Cisplatin+Paclitaxel

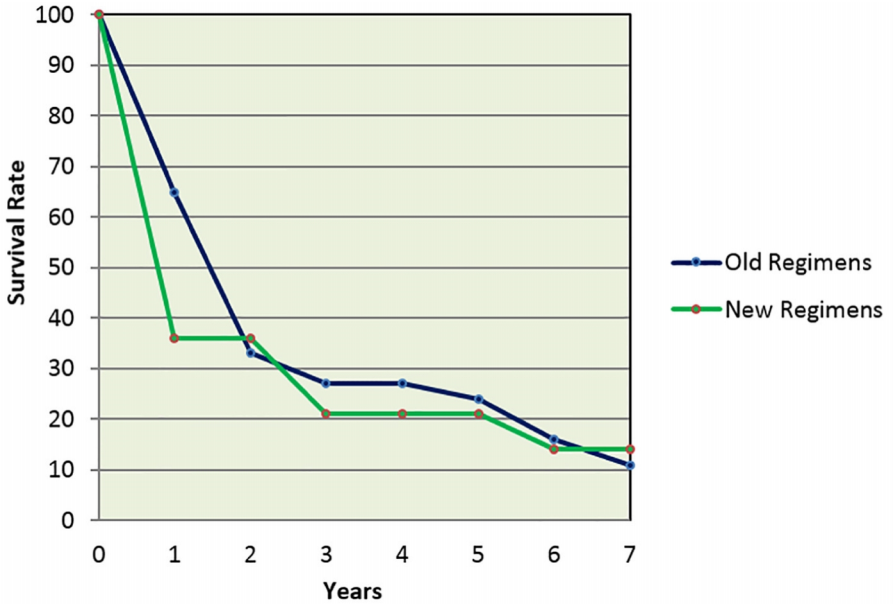

Figure 2. Kaplan–Meier survivals estimation of the overall survival for definitive chemo-radiation with old regimens and new regimens

The 3-year survival rate was: 21% (SE = 15) in patients who were treated with cisplatin chemo-radiation, 43% (SE = 33) for cisplatin with 5-FU chemo-radiation, 29% (SE = 23) for cisplatin with irinotecan chemo-radiation, and 14% (SE = 4) for cisplatin with paclitaxel chemo-radiation. The overall 3-year survival rate was 26% (SE = 14) and it was 27% (SE = 20) in patients who were treated with the old chemotherapy regimen and it was 21% (SE = 13) in patients who were treated with the new chemotherapy regimen. The 5-year survival rate was 17% (SE = 21) in patients who were treated with cisplatin chemo-radiation, 43% (SE = 43) for cisplatin with 5-FU chemo-radiation, 29% (SE = 30) for cisplatin with irinotecan chemo-radiation, and 14% (SE = 5) for cisplatin with paclitaxel chemo-radiation. The overall 5-year survival rate was 24% (SE = 28), and it was 24% (SE = 32) in patients who were treated with the old chemotherapy regimen, and it was 21% (SE = 21) in patients who were treated with the new chemotherapy regimen. The median survival time, 3-year survival rate, 5-year survival rate are shown in Table 2. According to the two-tailed Breslow test, cisplatin versus cisplatin with 5FU ($p = 0.54$), cisplatin versus cisplatin and irinotecan ($p = 0.85$) and cisplatin versus cisplatin with paclitaxel ($p = 0.026$) were compared. Then, the cisplatin scheme was only statistically significant better than cisplatin with paclitaxel scheme. According to the two-tailed Breslow test, cisplatin with 5FU versus cisplatin with irinotecan ($p = 0.61$), cisplatin with 5FU versus cisplatin and paclitaxel ($p = 0.028$) and cisplatin with irinotecan versus cisplatin with paclitaxel ($p = 0.36$) were compared. Then, cisplatin with 5FU scheme was only statistically significant better than cisplatin with paclitaxel scheme. There was not any statistically significant difference based on the two-tailed Breslow test between the old chemotherapy regimens (cisplatin or cisplatin and 5FU) and the new chemotherapy regimens (cisplatin with paclitaxel or cisplatin with irinotecan) ($p = 0.18$). The comparison analyses between chemotherapy regimens according to the two-tailed Breslow test are summarized in Table 3. Four patients of 41 patients (10%) in the old chemotherapy regimen group experienced leucopenia, and 6 patients of 14 patients (43%) in the new chemotherapy regimen group experienced leucopenia. Overall, the incidence of leucopenia was 18% in the patients. There was a statistically significant difference between the two regimens in leucopenia incidence ($p = 0.012$, OR = 6.93, 95% CI = 1.58 - 30.41) (Table 4).

Table 2. Survival time of 55 patients with SCC of esophagus who were treated with chemo-radiation

Type of chemotherapy	Median Survival Time months (95% CI[a])	3-year Survival Rate % (SE[b])	5-year Survival Rate % (SE)
Cis[c]	17 (12.6-21.3)	21 (15)	17 (21)
Cis+5-FU[d]	22 (5.6-38.3)	43 (33)	43 (43)
Cis+Irinotecan	27 (0-68)	29 (23)	29 (30)
Cis+Paclitaxel	5 (2.4-7.5)	14 (4)	14 (5)
Old Regimens	17 (11.8-22.1)	27 (20)	24 (32)
New Regimens	6 (4.1-7.8)	21 (13)	21 (21)
Overall	14 (8-19.9)	26 (14)	24 (28)

[a]CI: confidence interval; [b]SE: standard error; [c]Cis:cisplatin; [d]5-FU: 5-fluorouracil

Table 3. Analysis of the comparison between chemotherapy regimens in patients with SCC of esophagus who were treated with chemo-radiation according to the two-tailed Breslow test

Chemotherapy regimens	p-value
Cis[a]/Cis with 5-FU[b]	0.54
Cis/Cis+Irinotecan	0.85
Cis/Cis+Paclitaxel	0.026
Cis+5-FU/Cis+Irinotecan	0.61
Cis+5-FU/Cis+Paclitaxel	0.028
Cis+Irinotecan/Cis+Paclitaxel	0.36
Old Chemotherapy regimens/New Chemotherapy regimens	0.18

[a]Cis:cisplatin; [b]5-FU: 5-fluorouracil

Table 4. Analysis of the incidence of leucopenia in the old and new regimens in patients with SCC of the esophagus who were treated with chemo-radiation according to Fisher's exact test

Type of chemotherapy	Incidence of leucopenia; n (%)	Difference between the two regimens (with respect to leucopenia incidence), % (CI: 95%)	p-value	Odds Ratio, (CI: 95%)
Old regimen	4 of 41 (10)	33 (10-55)	0.012	6.93 (1.58-30.41)
New regimen	6 of 14 (43)			
Total	10 of 55 (18)			

4. Discussion

In this study, we compared the differences in survival and hematologic toxicity rates between the old generation regimens (cisplatin with or without 5-FU) and the new generation regimens (cisplatin with paclitaxel or cisplatin with irinotecan) in patients with non-metastatic esophageal SCC who were treated with definitive chemo-radiation. There was not any statistically significant difference between the old chemotherapy regimens and the new chemotherapy regimens ($p = 0.18$). Even hematological toxicity, including leucopenia events, was significantly lower for the old generation regimens group ($p = 0.012$). The literature concerning the effectiveness and toxicity of the new generation regimens compared with the old generation regimens (standard of care) is limited. Polee et al. determined that the use of carboplatin with paclitaxel as part of definitive chemo-radiation with median survival 11 months, and the leucopenia incidence rate of 77%. The findings were inconsistent with our study that showed median OS of 6 months and a leucopenia incidence rate of 43% in the new chemotherapy regimens group (15). Courrech and colleagues compared cisplatin with paclitaxel and cisplatin with 5-FU. The median OS was 15 months, which was similar in both treatment regimens. They did not report leucopenia of these chemotherapy regimens (16). The findings were inconsistent with our study that showed median OS in cisplatin with paclitaxel and cisplatin with 5-FU were 5 and 22 months, respectively. We also proved that cisplatin with the 5-FU scheme was statistically significant better than the cisplatin with paclitaxel scheme ($p = 0.028$). Blom et al. compared cisplatinum/5-FU and carboplatin/paclitaxel in the neoadjuvant setting and showed no difference in survival and overall toxicity, unlike our study (17). Honing et al. compared carboplatin with paclitaxel and cisplatinum with5-FU as definitive chemo-radiation. The median OS was 15 months for the entire group of patients, 16.1 months for the cisplatin with 5-FU group, and 13.8 months for the carboplatin with paclitaxel group (18). OS was similar in both treatment regimens. The findings of our study were consistent with their findings in that study. Wang et al. showed an overall 3-year survival rate of 60% in locally advanced esophageal cancer patients who were treated with carboplatin and paclitaxel as part of definitive chemo-radiation (19). The findings were inconsistent with our study that showed a 3-year OS rate of 14% in the cisplatin with paclitaxel group. However, they did not compare this regimen with other chemotherapy regimens. There were some limitations in our study. First, our study was a retrospective-analytical study such as all those inherent in a retrospective analysis. Second, the number of patients (55) was considered small for accurate analysis of predictive factors, although we had a long median follow-up time (72 months). However, the number of esophageal cancer patients receiving definitive chemo-radiation was limited because most of the patients were treated with esophegtomy. Third, the patients were not randomized, which could lead to differences in patients' characteristics and treatment between treatment chemotherapy regimen groups.

5. Conclusions

This retrospective-analytical study suggested that OS was similar in both the old and new chemotherapy treatment regimens in esophageal cancer patients who were treated with definitive chemo-radiation. Even so, the cisplatin scheme and cisplatin with 5Fu (old chemotherapy treatment regimens) were statistically significant better than the cisplatin with paclitaxel scheme. The old chemotherapy treatment regimens have fewer leucopenia events than the new chemotherapy regimens. These results suggest that the new chemotherapy regimens should be used with caution as an alternative for cisplatin or cisplatin with 5Fu, which are the standard of care in definitive chemo-radiation for esophageal cancer patients.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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