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Original article

Palliative Chemotherapy in Recurrent or Metastatic Squamous cell carcinoma of the head and neck, NEMROCK experience

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Background: Patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) have a poor prognosis with a median survival of 6 to 10 months. So treatment of these patients is primarily palliative. In this study we evaluated the results of 2 different chemotherapy regimens.
Patients and Methods: This is a retrospective study of 60 patients with R/M SCCHN recruited to Kasr Al-Aini Center of Clinical Oncology and Radiation Therapy (NEMROCK) from March 2007 till November 2011. Patients were treated either by Methotrexate (MTX) 40mg/m^2 weekly or by combination chemotherapy of Cisplatin/5-Fluorouracil (PF) (cisplatin 100 mg/m^2 as a 2-hour intravenous infusion on day 1 and an infusion of fluorouracil 1000 mg/m^2 per day for 4 days) every 3 weeks. Primary end point was overall survival while secondary end points were overall response rate, progression free survival and toxicity.
Results: Overall response rates in the MTX and PF arms were 12.5% and 32.14% respectively. PF regimen had significant superior progression free survival than MTX 3.25 months (95% 2.32 to 4.17) versus 1.5 months (95% 1.16 to 1.83) *P*= 0.01. There was no significant difference in overall survival between treatment arms. Median survival in patients receiving MTX and PF was 5 months (95% 4.17 to 5.83) and 6 months (95% 5.03 to 6.96) *P*= 0.08 respectively. Hematological toxicity was significantly higher in PF arm.
Conclusion: Combination chemotherapy Cisplatin/5-Fluorouracil had significant superior response rate, progression free survival but with an increased toxicity and non significant longer overall survival than single agent weekly methotrexate in recurrent or metastatic squamous cell carcinoma of the head and neck.

Key words: Squamous cell carcinoma, Head & neck, Cisplatin/5-fluorouracil, methotrexate.
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INTRODUCTION

Patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (R/M SCCHN) have a poor prognosis with a median survival of 6 to 10 months[1]. Selected patients with locally recurrent disease can be treated with a curative intent with locoregional therapies, such as salvage surgery and/or radiotherapy; however, the vast majority of patients die from their disease. Chemotherapy remains the cornerstone of treatment this setting[2].

According to the main suggested guidelines[3,4] a wide range of options of chemotherapy is proposed. Either single agent chemotherapy or combination regimens. Single agent as cisplatin, carboplatin, methotrexate, bleomycin, 5-fluorouracil, paclitaxel or docetaxel; while combination regimens as cisplatin or carboplatin backbone with 5-Fluorouracil and/or taxanes with a possible integration of a biological targeted therapy as cetuximab. The choice of chemotherapy regimen depends mainly on the performance status of the patient. The best results achieved were by the combination of Cetuximab plus Platinum–Fluorouracil with an overall survival of 10.1 months[5].

To date, there is limited data on chemotherapy outcomes in Egyptian patients with (R/M SCCHN). In order to evaluate and document our daily practice, we retrospectively analyzed the outcomes of chemotherapy in treatment of R/M SCCHN. The primary endpoint of this study was overall survival and the secondary endpoints were overall response rate, progression free survival and toxicity.

PATIENTS AND METHODS

This is a retrospective study of 60 patients with R/M SCCHN recruited to Kasr Al-Aini Center of Clinical Oncology and Radiation Therapy (NEMROCK) from March 2007 till November 2011.

Patients with R/M SCCHN after radical radiation therapy (as primary treatment or postoperatively with or

without concomitant platinum-based chemotherapy) not amenable to salvage surgery or radiation therapy were eligible. There were no restrictions on prior platinum-based chemotherapy. Upon review of patient's files, 60 cases were properly followed and documented.

The treatment schedule was as follows:

Arm I: Methotrexate (MTX) was injected weekly as an intravenous push at 40mg/m^2.

Arm II: Cisplatin/5-Fluorouracil (PF) was administered as cisplatin (at a dose of 100 mg/m^2 as a 2-hour intravenous infusion on day 1) and a continuous infusion of fluorouracil (at a dose of 1000 mg/m^2 per day for 4 days) every 3 weeks.

Statistical Methods:

Overall survival was calculated from treatment initiation to death or last follow-up. PFS was calculated from treatment initiation to disease progression or last follow-up, Response rate by RECIST criteria[6] and toxicity profile by the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0.7

Data were then analyzed statistically using SPSS Statistical package version 17 with calculation of mean, median and confidence interval. The Kaplan-Meier method was used for the calculation of the overall survival and progression free survival.

RESULTS

Between March 2007 and November 2011, sixty eligible patients were recruited. 32 patients received single agent chemotherapy methotrexate and 28 patients received combination chemotherapy Cisplatin/5-Fluorouracil. A total of 207 weekly MTX injections were recorded with a median of 5 injections and a range of two to sixteen. For PF regimen a total of 91 cycles recorded with a median of 3 cycles and a range of one to six per patient. Pretreatment characteristics of the 60 eligible patients are listed in Table (1). Two patients did not receive radiotherapy in PF regimen because both were laryngeal carcinoma who underwent total laryngectomy with no indication for adjuvant radiotherapy and then presented later on with distant metastases. We have to mention that 59.37% of patients receiving MTX have a performance status of 2 while 64.28% of PF have performance status of 0-1.

Efficacy:

Tumor response was assessed in all sixty patients as seen in Table (2). Overall response rates were 12.5%, and 32.14% in the methotrexate and Cisplatin/5-FU arm, respectively. PF regimen had significant superior median progression free survival than MTX 3.25 months (95% 2.32 to 4.17) vs 1.5 months (95% 1.16 to 1.83) respectively (*P*= 0.01). There was no significant difference in overall survival between treatment arms. Median survival in patients receiving MTX and PF was 5 months (95% 4.17 to 5.83) and 6 months (95% 5.03 to 6.96) respectively (*P*= 0.08). Progression free survival and overall survival are illustrated in Figure (1) and (2). Three patients in PF regimen with loco-regional recurrence underwent surgery for residual disease.

Safety:

Eight treatment related mortality occurred, 2 in arm I and 6 in arm II during treatment: five from infection, two from hemorrhage and one from cardiac cause. Hematological toxicity was significantly more in PF regimen (*P*= 0.01). Therefore, a dose reduction in 23 patients (82.14%) of PF regimen was monitored. Febrile neutropenia was recorded in 13 patients (46.42%) with 5 deaths encountered. Non hematological toxicity included vomiting and stomatitis mainly, creatinine elevation was significantly in PF regimen while transaminases elevation was significantly in MTX regimen. Grade 3 and 4 adverse effects are illustrated in Table (3).

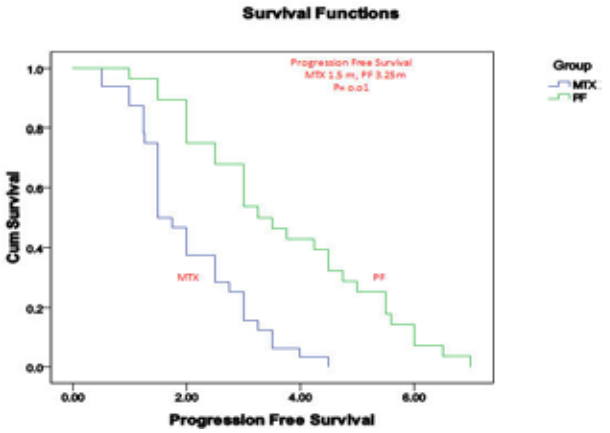

Figure 1: Kaplan-Meier curve of Progression Free survival for both treatment arms.

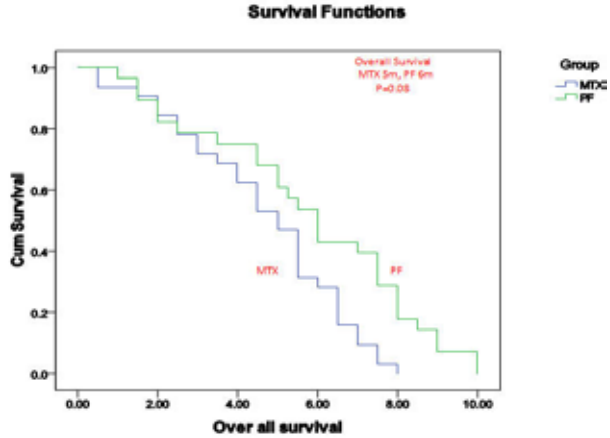

Figure 2: Kaplan-Meier curve of overall survival for both treatment arms.

Table 1: Baseline Characteristics of the Patients.

Variable	Arm I Methotrexate (N = 32)	Arm II Cisplatin/5-FU (N = 28)
Sex — no. (%)		
Male	27 (84.37)	24 (85.71)
Female	5 (15.62)	4 (14.28)
Age		
Median	64	58
[range]	[46-71]	[28-66]
ECOG performance status:		
- 0-1	13 (40.62)	18 (64.28)
- 2	19 (59.37)	10 (35.71)
Primary tumor site — no. (%)		
Oropharynx	7 (21.87)	9 (32.14)
Hypopharynx	9 (28.12)	5 (17.85)
Larynx	11(34.37)	9 (32.14)
Oral cavity	5 (15.62)	5 (17.85)
Extent of disease — no. (%)		
Only locoregionally recurrent	18 (56.25)	17 (60.71)
Metastatic with or without locoregional recurrence	14 (43.75)	11 (39.28)
Histologic type — no. (%)		
Well differentiated	3 (9.37)	4 (14.28)
Moderately differentiated	15 (46.87)	11 (39.28)
Poorly differentiated	13 (40.62)	11 (39.28)
Not specified or missing	1 (3.125)	2 (7.14)
Previous treatment — no. (%)		
Chemotherapy	20 (62.5)	19 (67.85)
Radiotherapy	32 (100)	26 (92.85)

Table 2: Overall Tumor Response

Parameter	Arm I Methotrexate (N = 32)	Arm II Cisplatin/5-FU (N = 28)
Complete response (CR)	0	1 (3.57)
Partial response (PR)	4 (12.5)	8 (28.57)
Stable disease (SD)	7 (21.87)	10 (35.71)
Progressive disease (PD)	21 (65.62)	7 (25)
Overall response (CR + PR)	4 (12.5)	9 (32.14)

Table 3: toxicity.

Adverse Effect	Arm I Methotrexate (N = 32)		Arm II Cisplatin/5-FU (N = 28)	
	Grade 3 No. (%)	Grade 4 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Anemia	-3 (9.37)	-	9 (32.14)	1 (3.57)
Leukopenia	- 5 (15.62)	-2(6.25)	11(39.28)	7 (25)
Neutropenia	- 6 (18.75)	-2(6.25)	15 (53.57)	10 (35.71)
Thrombocytopenia	-1 (3.12)	-	3(10.71)	-
Vomiting	4 (12.5)	-	5 (17.85)	-
Stomatitis	-11 (34.37)	-	6 (21.42)	2 (7.14)
Creatinine	-	-	2 (7.14)	-
Transaminases elevation	-7 (21.87)	-	1 (3.57)	-

DISCUSSION

Treatment of patients with R/M SCCHN is a hard task. In spite of all available treatment lines the prognosis is poor. After salvage surgery and radiation therapy and in the majority of patients, chemotherapy should be used with a palliative aim.1,2 In our country with limited resources, we prefer to use cost effective therapy in palliative settings. In this study we highlighted outcomes of our unit guideline as a center during the last 4 years.

Single agent methotrexate is considered to be the historical standard and has been most frequently investigated as a weekly intravenous regimen. It is a cost effective medication, easy to administer not requiring hospital admission and exhaustion of resources. A weekly dose of 40–60mg/m^2 of methotrexate were considered standard therapy with variable response rate recorded between 3.9–25%. Overall survival reported with MTX was around 6 months[8-11]. In our study, we witnessed 12.5% response rate and 5 months median overall survival which is comparable with published data.

During the last decade, Cisplatin/infusional 5-FU (PF) regimen gradually became as the most popular combination chemotherapy regimen in patients with R/M SCCHN in view of its higher response and superior PFS. Non-randomized trials indicated a better outcome than what was observed with single-agent treatment, at least with respect to OR rates including CR/PR rates. In a number of randomized phase III trials performed in the 1990s, PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not in statistically significant survival advantage, and this gain in response rates was obtained at the cost of more toxicity[12,13]. In a phase III trial, 277 patients were randomized to receive PF, carboplatin–5-FU (CF) or standard dose MTX. PF had significantly higher response rate than MTX (P= < 0.001), but the comparison of PF with MTX was of only borderline significance (P= 0.05). And again, median survivals were similar for all three treatment groups[8]. Which is comparable to our results where PF had significant more response rate, progression free survival than MTX. However, there was no statistically survival advantage.

Toxicity of PF regimen is a major concern, we witnessed six (21.42%) treatment related mortality during the first two cycles in contrast with data reported in Intergroup Trial of the Eastern Cooperative Oncology Group where 6.7% of patients had toxic death from treatment[14]. So, we have to give this toxic regimen to patients with good performance status (0-1)

with some precautions like 25% dose reduction for the initial cycles, careful follow-up, and administration of prophylactic growth factors support especially in elderly patients. Another important issue is the renal toxicity commonly encountered with PF regimen, we noticed two patients with grade 3 serum creatinine elevation. In such situation, increasing hydration carefully especially with patients with borderline cardiac function is recommended. Otherwise, substitution of Cisplatin with carboplatin especially when creatinine clearance drops to ≤ 50 mL/min.

Although taxanes have considerable activity in R/M SCCHN, no randomized studies performed in the palliative setting have demonstrated a significant improvement in overall survival[10,15]. In a phase III trial 218 patients with R/M-SCCHN were randomized to either PF or cisplatin–paclitaxel. There was no significant difference in overall survival, response rate or toxicity profile[14].

The addition of the monoclonal antibody cetuximab to platinum and Fluorouracil appear to be the standard of care for patients with good performance status. In a phase III trial, the addition of cetuximab was shown to improve median survival from 7.4 to 10.1 months and median progression-free survival from 3.3 to 5.6 months with significant acceptable toxicities[5]. however, availability of cetuximab in our governmental center especially for a palliative treatment of patients with R/M SCCHN is quiet problematic.

CONCLUSION

In conclusion, the outcome of patients with R/M SCCHN is still dismal. We documented that combination chemotherapy PF had significant superior response rate, progression free survival and non significant longer overall survival than single agent MTX. The choice of chemotherapy depends on disease symptoms and performance status. If rapid improvement in symptoms is desired with good performance status, combination therapy is preferable; however, if non-symptomatic disease in a poor performance patient, use single agent might be more valuable. Novel non-toxic agents or approaches for the treatment of R/M-SCCHN are eagerly awaited.

Disclosure:

The authors report no conflicts of interest in this work.

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