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Concomitant chemoradiotherapy with low-dose weekly gemcitabine for nonmetastatic unresectable pancreatic cancer

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Background/aims: *This study aimed to demonstrate the efficacy and tolerability of low-dose weekly gemcitabine as a radiosensitizer in unresectable pancreatic cancer patients treated with chemoradiotherapy.* ***Methods:*** *Twenty-four histologically confirmed pancreatic carcinoma patients (female/male: 10/14, median age: 60) were evaluated. Seven (29%) patients received gemcitabine either as a single agent or in combination prior to chemoradiotherapy. Concurrent 75 mg/m² gemcitabine was infused weekly. Radiotherapy was delivered to the primary tumor and positive lymphatics with 3D-conformal radiotherapy to a total dose of 4500 cGy. Local progression-free survival, distant metastasis-free survival and overall survival were evaluated by Kaplan-Meier method.* ***Results:*** *Median follow-up was 36 weeks. Median local progression-free survival, distant metastasis-free survival and overall survival were 22 weeks (95% confidence interval [CI]: 5-59 weeks), 19 weeks (95%CI: 6.9-31 weeks) and 36 weeks (95%CI: 28-43 weeks), respectively. All patients completed radiotherapy as scheduled. Concurrent gemcitabine was given fully in 58.3% of patients. Gemcitabine was terminated in four (16.6%) patients due to grade 3 neutropenia (n=1), grade 3 nausea/vomiting (n=2) or patient's reluctance (n=1). Patients with local response and stable disease to chemoradiotherapy revealed a median survival of 39 weeks (95%CI: 30-47.9 weeks) compared to 36 weeks (95%CI: 9.7-62.2 weeks) in patients with locally progressive disease (p=0.52). Pain was improved in 50% of patients.* ***Conclusions:*** *Weekly low-dose radiosensitizing gemcitabine is effective and safe in unresectable pancreatic cancer patients.*

Key words: Chemoradiation, gemcitabine, low dose, pancreatic cancer, unresectable

Rezeke edilemeyen pankreas kanserinde eş zamanlı düşük doz gemsitabinle kemoradyoterapi

Amaç: *Bu çalışmada kemoradyoterapiyle tedavi edilen rezeke edilemeyen ve metastatik olmayan pankreas kanserinde radyosensitizan amaçlı düşük doz gemsitabininin, etkinliği ve tolerabilitesi araştırıldı.* ***Yöntem:*** *Histolojik olarak tanı konmuş 24 pankreas kanseri hastası (kadın/erkek: 10/14; ortanca yaş 60) değerlendirildi. Yedi (%29) hastada gemsitabin, tek başına ya da diğer ajanlarla birlikte indüksiyon amaçlı kullanılmıştı. Eş zamanlı gemsitabin 75 mg/m² olarak haftalık uygulandı. Üç boyutlu konformal radyoterapi ile primer tümöre ve pozitif lenfatiklere 4500 cGy verildi. Lokal progresyonsuz sağkalım, uzak metastazsız sağkalım ve tüm sağkalım Kaplan-Meier metodu ile hesaplandı.* ***Bulgular:*** *Ortanca takip 36 hafta idi. Ortanca lokal progresyonsuz sağkalım, uzak metastazsız sağkalım ve tüm sağkalım sırasıyla 22 hafta (%95 GA 5-59 hafta), 19 hafta (9%5 GA 6.9-31 hafta) ve 36 hafta (%95 GA 28-43 hafta) idi. Bütün hastalar radyoterapiyi planlandığı dozda tamamladı. Eş zamanlı gemsitabin tam olarak %58.3 hastaya uygulandı. Gemsitabin dört (%16.6) hastada derece 3 nötropeni (n=1), derece 3 bulantı/kusma (n=2) ve hastanın reddi (n=1) nedeniyle kesildi. Kemoradyoterapi sonrası lokal tümörü cevap veren ya da stabil kalan hastalarda ortanca sağkalım 39 hafta (%95 GA 30-47.9 hafta) iken progresyon gösterenlerde 36 hafta (%95 GA 9.7-62.2 hafta) idi (p=0.52). Hastaların %50'sinde ağrı palyasyonu sağlandı.* ***Sonuç:*** *Rezeke edilemeyen pankreas kanserinde radyosensitizan haftalık düşük doz gemsitabin etkili ve güvenlidir.*

Anahtar kelimeler: Kemoradyoterapi, gemsitabin, düşük doz, pankreas kanseri, rezeke edilemeyen

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INTRODUCTION

Pancreatic cancer is a rare disease that accounts for 2% of all cancer cases and 6% of cancer deaths per year (1). Most patients are diagnosed in the locally advanced or metastatic stage and the mortality rate is high, in that about 83% of newly diagnosed pancreatic cancer cases in 2009 will die (2). Although surgery is the only possibility of cure, only about 20% of them are resectable at diagnosis (3). A surgically unresectable tumor comprises the locally advanced pancreatic cancers with involvement of the celiac axis or superior mesenteric artery (4).

Fluoropyrimidine-based concurrent chemoradiotherapy (CRT) increases overall survival in locally advanced pancreatic cancer patients compared to radiotherapy (RT) alone, and this has been supported previously by several randomized group trials like the Gastrointestinal Tumor Study Group (GITSG) and the Eastern Collaborative Oncology Group (ECOG) (5,6). Despite the encouraging results for combined treatment, survival improvement is far from that observed in resectable series, and new therapeutics are required.

Over the last 10 years, gemcitabine (GEM), a fluorine-substituted cytarabine analog, has become a standard of chemotherapy in metastatic and non-metastatic advanced pancreatic carcinoma (7). It has been shown in preclinical studies that GEM is also a relevant radiosensitizer (8). Li et al. (9) reported in their small phase III trial that GEM-based CRT was more effective than 5-fluorouracil (5-FU)-based CRT. GEM has become more popular and effective as a radiosensitizer. However, both hematological and non-hematological toxicities are the major concern for GEM-based treatments. In several phase I and phase II trials, concurrent GEM has been administered in different doses; however, the optimal radiosensitization dose is still not clear (10-15).

In this retrospective analysis, we aimed to report and discuss our experience with low-dose weekly radiosensitizing GEM in terms of efficacy and toxicity.

MATERIALS AND METHODS

Twenty-four patients (14 males, 10 females) with nonmetastatic unresectable pancreatic head adenocarcinoma who applied to Marmara University Hospital Radiation Oncology Department were included in this retrospective analysis. Median age was 60 years (range: 42-76 years) and baseline Karnofsky Performance Status score was ≥60 for all patients. Pre-CRT evaluation of the primary tumor was done with computerized tomography (CT), and distant metastasis was evaluated in the chest and upper abdominal CT. Before RT, exploratory laparotomy and surgical gastrointestinal by-pass were done in 13 (54%), whereas biliary stent was done in 4 (16.6%) patients. Histopathologic diagnosis was done with a CT or ultrasound-guided biopsy in 7 (29%) patients, with incisional biopsy during laparotomy in the rest.

Prior to CRT, 7 (29%) patients received 1 to 5 cycles of GEM (median: 2 cycles) either as a single agent or in combination with cisplatin or 5-FU. Following CRT, patients received GEM-based chemotherapy in case of disease progression.

Gemcitabine (GEM) 75 mg/m^2/week was infused within 30 minutes starting on day 1 and continued weekly over five weeks. RT was delivered with a high-energy linear accelerator using 6-18 MV photons, and the total dose was 4500 cGy in 25 fractions with a 180 cGy fraction dose. 3D conformal treatment planning was done by using the three-field technique (single anterior and two lateral fields) in all patients. Clinical target volumes included the primary tumor and radiologically involved regional lymphatics with 2 cm margin. Physical examination, total blood counts and side effects were recorded weekly, whereas liver and kidney function tests were obtained every three weeks. GEM dose was reduced in patients that experienced grade 3-4 toxicity, and all acute toxicities were evaluated according to common toxicity criteria (CTC) v2.0 (16).

First response assessment was done with upper abdominal CT scan six weeks after CRT and repeated every eight weeks thereafter. At least 25% of increase in tumor diameter was defined as progression, ≥50% of reduction as partial response, and the rest as stable disease.

Statistical analysis

Local progression-free survival (LPFS) was defined as the time from the beginning of CRT to the clinical and/or radiological progression, while distant metastasis-free survival (DMFS) was the period from histological diagnosis to first appearance of disease relapse out of the RT field. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any cause or the last follow-up. All survival curves were plot-

ted using the Kaplan–Meier method (17) and survival differences for treatment were analyzed using the log-rank test. A p-value less than 0.05 was considered statistically significant.

RESULTS

Survival analysis

There was no progression observed at the end of CRT, and there were no treatment- related deaths. The median follow-up was 36 weeks (range: 13-103 weeks). At the time of analysis, all patients died due to disease progression except two patients who died with gastrointestinal bleeding at the 9th and 25th weeks following CRT. One of these patients had adrenal metastasis and the other had no sign of any local or distant disease progression. Ten (41.6%) local progressions, 14 (58.3%) liver and 1 adrenal metastases were detected. Primary tumor regression was observed in 3 (12.5%) patients, while 11 (45.8%) patients had stable tumor size on radiological imaging. All 8 patients who received induction chemotherapy developed liver metastasis during the follow-up; however, the primary tumors were stable in the majority (85%). Clinical benefit with improvement in pain was achieved in 12 (50%) patients.

Median LPFS, DMFS and OS were 22 weeks (95% confidence interval [CI]: 5-59 weeks), 19 weeks (95%CI: 6.9-31 weeks) and 36 weeks (95%CI: 28-43 weeks), respectively (Figure 1). Median LPFS in 14 patients who received concurrent GEM without interruption was not significantly different from patients in whom GEM was stopped (17 weeks, 95%CI: 5-60 weeks vs 16 weeks, 95%CI: 4-50 weeks; p=0.17). Patients with local response and stable disease to CRT demonstrated a median survival of 39 weeks (95%CI: 30-47.9 weeks) vs 36 weeks (95%CI: 9.7-62.2 weeks) in patients with local progressive disease (p=0.52). OS was better in patients who received induction chemotherapy (48 weeks, 95%CI: 30.6-65.3 weeks) vs patients who had not received induction chemotherapy (36 weeks, 95%CI: 30.6-41.3 weeks), but the difference was not statistically significant (p=0.62).

Toxicity analysis

Radiotherapy (RT) was completed as planned in all patients. The median total dose of concurrent GEM was 675 mg (range: 270-810 mg), and it was administered in 14 (58.3%) patients without any interruption until the last week of RT. Grade 2 nausea was present in 25%, grade 2 diarrhea in 21%, grade 2 vomiting in 19%, and gastric symptoms in 12.5%. GEM was temporarily stopped due to neutropenia (n=3), nausea/vomiting (n=2) or hyperbilirubinemia (n=1), and was terminated in 4 (16.6%) patients due to grade 3 neutropenia (n=1), grade 3 nausea/vomiting (n=2) or patient's reluctance (n=1) at the median 4th week of RT (range: 3rd - 5th week).

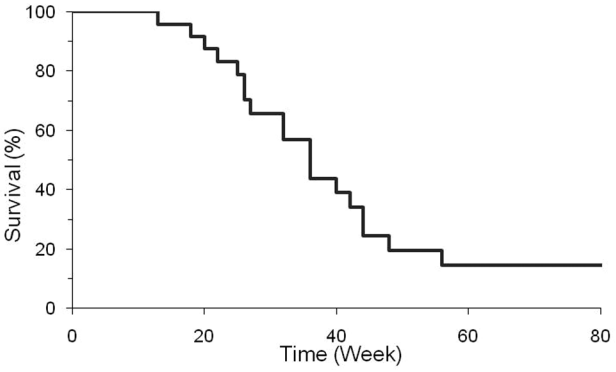

Figure 1. Overall survival.

DISCUSSION

Combined CRT became the standard treatment after the GITSG study for pancreatic cancer (5), and 5-FU-based chemotherapy is still the reference chemotherapeutic agent for combination with RT (5,6). However, pancreatic tumors are known as relatively radioresistant. One possible reason is the high level of hypoxic tumor fraction (18), which allows more clonogenic cells to conceal under this condition. Hence, more potential radiosensitizing agents are required to improve the poor prognosis. Although the radiosensitizing effect of GEM is not completely understood, the mechanism of action is through depletion of the deoxyadenosine triphosphate pool and incorporation into DNA with subsequent inhibition of DNA synthesis and repair (19).

The combination of GEM and RT may lead to an improved therapeutic outcome, but the major problem is the prominent increase in toxicity. In phase I and phase II studies, concomitant GEM was administered in doses between 250 and 500 mg/m^2/w (10-15). These studies showed that the side effects enhanced with dose escalation, without any distinct improvements in response. Crane et al. (10) compared 5-FU and GEM in their study, and they observed more severe toxicity in the GEM arm. They also concluded no significant survival advantage (11 mo vs 9 mo), but enhanced to-

xicity compared to the 5-FU arm. Phase I studies testing the low doses also reported enhanced toxicity without any survival endpoint improvements. Poggi et al. (11) reported in their phase I study that the maximum weekly tolerated dose of GEM was 440 mg/m^2 with the median OS of 39 weeks, which is similar to our study. Even at the low doses, grade 3-4 toxicity was frequent. In a phase I study (12), the maximum twice weekly tolerable dose was 50 mg/m^2, and the authors observed one gastrointestinal bleeding one month after the therapy. Blackstock et al. (13) reported that neutropenia and thrombocytopenia were not uncommon, with grade 3 neutropenia in 50%, grade 3 thrombocytopenia in 50% and grade 3 nausea/vomiting in 16% with 60 mg/m^2 biweekly GEM. In our study, acute grade 3 toxicity was present in 12.5% (neutropenia, n=1; nausea/vomiting, n=2). However, we also observed two gastrointestinal bleedings during follow-up.

In a phase II study, Cengiz et al. (14) administered concurrent GEM at 400 mg/m^2 weekly with 50.4 Gy RT. Grade 3 toxicity was seen in 18%, and in 82% of the patients, primary tumor was either totally/partially regressed or remained stable. Concomitant schedule compliance rate was 55%. In our study, the compliance to GEM and response rate of tumor were 59% and 58%, respectively. Even though the RT (45 Gy vs 50.4 Gy) and weekly GEM (75 mg/m^2 vs 400 mg/m^2) doses were lower in our study, median OS was comparable (36 weeks vs 8.7 mo). In the aforementioned trial (14), the authors also pointed to the possible geographic and genetic differences that may influence the tolerability of concurrent GEM. A phase I study from our country supported this argument (15). Yavuz et al. (15) concluded that the maximum tolerated dose of twice-weekly GEM should not exceed 90 mg/m^2.

We also observed that local response including stable disease improves the median survival (39 weeks vs 36 weeks). Despite the lack of significance, this result shows the local control importance in this systemic aggressive disease. Moreover, we observed 50% clinical pain relief during follow-up. Therefore, we think that RT should be considered in the treatment of locally advanced pancreatic cancer patients.

Based on the studies, it appears that dose escalation for concurrent GEM may not be an effective strategy because toxicity increases without any marked increase in survival results. Therefore, researches on newer targeted therapies that modulate cellular signaling or repair processes rather than inducing direct cytotoxicity may be rational.

In conclusion, since geographic differences may influence the tolerability of concurrent CRT, we think that weekly 75 mg/m^2 GEM may be a reasonable radiosensitizing dose in our patients. The toxicity seems acceptable and results are not inferior to results with high doses reported previously in the literature.

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