RESEARCH

COMPARISON OF THREE FIRST-LINE TREATMENTS IN ADVANCED PANCREATIC CANCER PATIENTS OLDER THAN 65 YEARS OF AGE: SINGLE-CENTRE EXPERIENCE

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Abstract

Introduction: Elderly advanced pancreatic cancer patients are frequently undertreated due to comorbidities, age, lack of evidence-based clinical practice guidelines for senior patients and patient's or physician's preference. An optimal, less toxic and most efficacious first-line chemotherapy regimen should be elucidated. The present study aimed to compare the efficacy and toxicity profiles of three first-line treatment regimens and describe prognostic factors in elderly pancreatic cancer patients.

Materials and Method: Patients of an age >65 years with histologically confirmed metastatic pancreatic adenocarcinoma not amenable to curative surgical resection were included in the study. Efficacy and toxicity profiles of FOLFIRINOX (Group A, 16 patients), cisplatin-gemcitabine combination therapies (Group B, 16 patients) and gemcitabine monotherapy (Group C, 15 patients) in elderly patients with advanced pancreatic cancer were evaluated retrospectively.

Results: There was no difference between the groups in terms of disease control rates, overall survival, and progression-free survival. Age, primary tumour resection, tumour grade and use of second-line chemotherapy were not found to be independently prognostic on overall survival (OS). Younger age <70 (p=0.028) and cisplatin-gemcitabine chemotherapy positively prognostic on OS (p=0.011) whereas liver involvement was negatively prognostic on OS (p=0.046). The toxicities of the groups were not different from each other but the hospitalization was statistically higher in FOLFIRINOX group.

Conclusion: The study revealed that there are no differences in disease control rates and adverse events of three regimens but showed increased overall survival with cisplatin–gemcitabine combination in elderly patients with pancreatic cancer.

Key words: Pancreatic cancer; Therapeutics; Geriatrics.

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ARAŞTIRMA

ALTMIŞ BEŞ YAŞ VE ÜZERİ METASTATIK PANKREAS KANSERİ HASTALARINDA BİRİNCİ SIRA ÜÇ FARKLI TEDAVININ KARŞILAŞTIRILMASI: TEK MERKEZ DENEYİMİ

Öz

Giriş: Yaşlı metastatik pankreas kanseri hastalarında ileri yaş, yandaş hastalık varlığı, yaşlı hastalar için kanıta dayalı klinik uygulama kılavuzlarının olmaması, hastanın kendi tercihi veya hekimin tercihi nedenleriyle daha az tedavi uygulanmaktadır. Bu hastalarda en az toksite ile en fazla etki gösterecek optimal ilk sıra tedavilerin tanımlanmasına ihtiyaç vardır. Bu çalışmadaki amacımız yaşlı metastatik pankreas kanserli hastalarda üç farklı birinci sıra tedavi rejiminin etkinlik ve toksite açısından karşılaştırılması ve prognostik faktörlerin tanımlanmasıdır.

Gereç ve Yöntem: Çalışmaya küratif cerrahi rezeksiyona uygun olmayan histolojik olarak doğrulanmış metastatik pankreatik adenokarsinomlu 65 yaş ve üstü hastalar dahil edildi.Metastatik pankreas kanseri olan yaşlı hastalarda FOLFIRINOX (Grup A, 16 hasta), sisplatin-gemsitabin kombinasyon tedavisi (Grup B, 16 hasta) ve gemsitabin monoterapisinin (Grup C, 15 hasta) etkinlik ve toksisite profilleri retrospektif olarak değerlendirildi.

Bulgular: Gruplar arasında hastalık kontrol oranları, genel sağkalım ve progresyonsuz sağkalım açısından fark izlenmedi. Yaş, primer tümör rezeksiyonu , tümör gradı ve ikinci basamak kemoterapinin kullanımı; genel sağkalım (OS) üzerine etkili bağımsız prognostik faktör olarak bulunmadı. Daha genç yaş <70 p=0.028) ve sisplatin-gemsitabin kemoterapisi kullanmak (p=0.011) OS üzerine etkili pozitif prognostik faktör, karaciğer tutulumu ise OS üzerine etkili negatif prognostik faktör olarak izlendi (p=0.046).Grupların toksisiteleri birbirinden farklı değildi, ancak hastaneye yatış FOLFIRINOX grubunda istatistiksel olarak daha yüksek olduğu belirlendi.

Sonuç: Çalışma, hastalık kontrol değerleri ve advers olaylar açısından üç rejim arasında bir fark olmadığını ortaya koydu; ancak yaşlı pankreas kanseri hastalarında sisplatin / gemsitabin kombinasyonu ile genel sağ kalım artışı gösterildi.

Anahtar Sözcükler: Pankreas kanseri; Tedavi; Geriatri.

INTRODUCTION

Pancreatic cancer (PC) is the seventh leading cause of cancer deaths, with 458,918 new cases and 432,242 new deaths in 2018 (1). It is most commonly diagnosed in elders aged >65 years (2). Most of the patients are unresectable and resistant to targeted therapies and immunotherapies (3, 4). Main treatment options for advanced PC are still cytotoxic chemotherapeutic regimens (5). Gemcitabine became the standard first-line regimen in advanced PC since Burris et al. showed improved median overall survival (m OS) (6). Addition of cisplatin to gemcitabine and new treatment combinations have been investigated (7-10).

Age-specific incidence of PC is increasing among patients >70 years of age but clinical trials, even in new trials, excluded or included very few patients older than 70 years of age (7-10). Elderly patients with advanced PC are frequently undertreated due to comorbidities, age, lack of evidence-based clinical practice guidelines for senior patients and patient's or physician's preference (11, 12). Although clinical benefits have been demonstrated with combination therapies (7, 9, 10), older patients are still being treated mostly with single-agent chemotherapy or best supportive care. There are few reports that compare the efficacy and safety of first-line monotherapy and combination therapies in older patients.

The present study aimed to compare efficacy and toxicity profiles of three different chemotherapy regimens in patients with advanced PC aged ≥65 years. The second aim was to describe prognostic factors affecting OS or PFS in patients with advanced PC aged ≥65 years. From this point of view, new studies investigating different dosages and combinations of chemotherapy are necessary for determining the best treatment choice.

MATERIALS AND METHOD

Study design and patients

This retrospective study was conducted at single medical oncology centre in Turkey. The study protocol was approved by the local ethics committee (Approval No: 12/12, dated 05/02/2019). Patients of an age >65 years with histologically confirmed metastatic pancreatic adenocarcinoma not amenable to curative surgical resection were included in the study. Treatments with FOLFIRINOX [oxaliplatin (85 mg/m^2), irinotecan (180 mg/m^2), 5-FU (400 mg/m^2 bolus and 2400 mg/m^2 46-hour continuous infusion) and leucovorin (400 mg/m^2) biweekly], cisplatin–gemcitabine (cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 weekly on day 1 and 8 in every 21-day cycle) or only gemcitabine (1000 mg/m^2 once a week for 2 weeks in 3-week cycles) were compared. Treatments were continued until any progression or development of an adverse event. No prior systemic therapy or radiotherapy was allowed. Brain metastases were included unless symptomatic. Primary tumour resections (PTRs) were not excluded if there was measurable extra-pancreatic disease. Adequate haematological, hepatic and renal functions were also required. Data of 47 patients treated between July 2013 and September 2018 were included. Patients were analysed in three treatment groups: those who received FOLFIRINOX were considered as group A, those who received cisplatin–gemcitabine were group B and those who received only gemcitabine were group C. OS, defined as the time from diagnosis to death, was the primary endpoint of the study. Secondary endpoints were PFS, response rates and adverse events. PFS is defined as the time from first treatment date to documented progression or death. Disease control rate (DCR) is defined as the sum of the partial response, stable disease and complete response.

Radiological response was assessed in every 3 cycles or in case of finding a clinical progression using Response Evaluation Criteria in Solid Tumours (version 1.1).

Toxicity was assessed in every cycle. Toxic effects were graded according to Common Termi-

nology Criteria for Adverse Events which was used at the time of treatment.

Statistical methods

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro–Wilk test. Descriptive analyses were presented using median (min–max) or n (%), where appropriate. Categorical data were analysed using Pearson's chi-squared test. The Kruskal–Wallis test was used for comparison of non-parametric variables between groups. OS and PFS were estimated using the Kaplan–Meier method. The log-rank test was used to compare the survival differences. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to explore prognostic factors for PFS and OS. The variables which showed significant association with OS or PFS in the univariate analyses were further tested in the multivariate model. Hazard ratios (HRs), with corresponding 95% confidence intervals (95% CIs), were reported. A p-value of <0.05 was considered statistically significant.

RESULTS

Patient demographics

The baseline characteristics of 47 patients are outlined in Table 1. Age (p=0.603), gender (p=0.296), Eastern Cooperative Oncology Group performance status (ECOG PS) (p=0.088), tumour size (p=0.559) and metastatic areas were similar in the three treatment groups (Table 1). Most of the tumours were located in the pancreatic head region (55.6%) and did not differ in the three groups (p=NA). PTR was performed in 55.3% of patients. Groups B and C had more PTR cases than group A (62.5% vs 73.3% vs 31.3%, respectively; p=0.048). Median number of treatment cycles of groups were similar [4 cycles (range 1–12) in group A, 4 cycles (range 1–8) in group B and 2 cycles (range 1–6) in group C; p=0.345]. Number of patients who received second-line chemotherapy after progression were similar in the three groups (p=NA) and constituted 27.7% of patients. The most commonly used second-line treatment was the nab-paclitaxel/gemcitabine combination (58.3%), followed by FOLFIRINOX (25%) and cisplatin–gemcitabine (16.7%) combination treatments.

Efficacy

DCRs were similar in groups B and C, which were higher than that in group A (p=NA) (Table 2). The median OS (m OS) was 11 months in group A, 17 months in group B and 8 months in group C (p=0.164). The median PFS (m PFS) was 3 months in group A, 6 months in group B and 4 months in group C (p=0.193) (Table 2, Figure 1). Patients <70 years of age had a longer m OS (p=0.028). PTR improved both m OS (p=0.006) and m PFS (p □ 0.001) (Table 3). Gender (p=0.918), ECOG PS (p=0.789), tumour localisation (p=0.213), lymphovascular invasion (p=0.178), perineural invasion (p=0.734), lung metastases (p=0.827), brain metastases (p=0.872), bone metastases (p=0.420) and lymph node metastases (p=0.599) did not affect the OS. Patients who received second-line treatment had a longer OS (16 months; 95% CI, 13.74–18.26) than that of those who did not (7 months; 95% CI, 5.44–8.56) (p=0.031), but second-line chemotherapy type did not show any difference on behalf of OS. Patients who received nab-paclitaxel and gemcitabine as second-line treatment had an m OS of 17 months (95% CI, 9.3–24.7); those who received FOLFIRINOX had an m OS of 17 months (95% CI, 15.4–18.6) and those who received cisplatin and gemcitabine had an m OS of 11 months (95% CI, NA) (p=0.198). Survivals were also not influenced by adverse events except febrile neutropenia (Table 3).

Prognostic factors affecting Progression Free Survival

Multivariate Cox proportional hazards model was performed to define the factors independently influencing PFS. Primary tumour resection (PTR)

was predicted to have a better PFS (HR: 0.128; 95% CI, 0.042–0.388, p<0.001). Age (p=0.155), tumour size (0.229), grade (0.978), liver involvement (p=0.319), first line chemotherapy cycle (p=0.118), febrile neutropenia (FEN) adverse events (p=0.230) were not found independently prognostic for PFS.

Prognostic factors affecting Overall Survival

Multivariate Cox proportional hazards model was performed to define the factors independently influencing OS. Age, PTR, tumour grade and use of second-line chemotherapy were not found to be independently prognostic of OS (p=0.469, 0.214, 0.189 and 0.065, respectively). Patients who had liver metastases were predicted to have a worsened overall survival (HR=3.251; 95% CI, 1.021–10.351, p=0.046). Patients who were administered more than 4 cycles of first-line chemotherapy had better overall survival (HR=0.327; 95% CI, 0.119–0.898, p=0.030). Use of cisplatin–gemcitabine chemotherapy was predicted to have better overall survival with regard to FOLFIRINOX (HR=0.213; 95% CI, 0.065–0.699, p=0.011). Multivariate analysis showed significant results in cisplatin + gemcitabine arm, but no difference was observed between groups in univariate analysis. This is thought to be due to presence of interactions which is part of suppression of one variable by another.

Adverse events

Table 4 summarises the adverse events. The main differences between the three groups were observed in the incidence of Grade 3–4 neutropenia; Grade 3–4 thrombocytopenia and febrile neutropenia. However, the statistical significance of these differences was not applicable. There were more frequent hospitalisations due to treatment toxicity in group A compared with that in groups B and C (p=0.018).

DISCUSSION

Treatment of advanced PC has improved recently. Kuroda et al. (12) reported 895 patients with unresectable PC, which included 659 elderly patients aged ≥65 years. They found that the median survival was shorter in the elderly group as compared to that in the younger group (181 vs 263 days, p=0.0001). Only 52.2% of elderly patients received chemotherapy, and in the treated subgroup, median survivals were not much different in elderly and younger groups (274 vs 333 days, p=0.09). This trial supported the idea that elderly patients with PC were able to benefit from and tolerate the treatments similar to the young people. Historic agent gemcitabine showed more clinical benefits/symptom relief and modest survival improvement with minimal toxicities (6) compared with 5-FU, even in fragile patients. Later, all new agents and combination treatments were compared to this historic gemcitabine monotherapy. A recent PRODIGE-4 trial (9) showed an improvement in m OS in the FOLFIRINOX arm compared to that in gemcitabine (m OS 11 vs 6.8 months, respectively; HR for death, 0.57; 95% CI, 0.45–0.73; p<0.001), and an MPACT trial (10) proved the first-line superiority of nab-paclitaxel/ gemcitabine over gemcitabine (m OS 8.5 vs 6.7 months, respectively; HR for death, 0.72; 95% CI, 0.62–0.83; p<0.001), which changed the standard treatment to combination therapies. However, these intensive chemotherapies were considered in fit patients who comprised only a small portion of the elderly group. In addition, 28% of elderly patients accrued to PRODIGE-4, in which elderly patients were under-represented and which could not report any data about safety of nab-paclitaxel/gemcitabine in elderly patients. However, 42% of patients accrued to MPACT were older than 65 years and could report acceptable toxicity in elderly patients (10).

Although there are many investigations for the best first-line chemotherapeutic option with a small survival benefit in advanced PC, it is still controversial and undetermined for the elderly patients. There are no guidelines for treatment in elderly patients with PC because the likelihood of

receiving standard chemotherapy is lower than in younger patients (13). To balance the toxicity and treatment advantage in elderly patients with advanced PC, proper treatment agents should be chosen, and dose reductions or delays and supportive treatments should be applied, if necessary. The knowledge about chemotherapy in elderly patients with advanced PC was obtained from retrospective, post-hoc and subset analysis of investigations. PAMELA70 is an ongoing phase II multicentre prospective trial enrolling chemo-naïve elderly patients with advanced PC, in which efficacy and tolerance of dose-adjusted FOLFIRINOX will be evaluated (14).

The cisplatin–gemcitabine combination has been tested in several studies (7, 8, 15-20). The GOIM study (7) first described the cisplatin–gemcitabine combination and reported an increased overall response rate (ORR) from 9.2% (95% CI, 3–20) with gemcitabine to 26.4% (95% CI, 15–40) (p=0.02) with the combination. Median OS (p=0.43) and toxicities were similar. GIP-1 study (15) tested the same regimens in 2010 and found no benefit in survival with the combination treatment. Italian GISCAD study investigated cisplatin 35 mg/m^2–gemcitabine 1000 mg/m^2 weekly for 2 consecutive weeks out of every 3 weeks. They reported an ORR of 9% (95% CI, 10–11) with an m OS of 5.6 months (17). Another German study researched different dosages of cisplatin–gemcitabine combination and showed insignificant survival advantages with combination when compared to gemcitabine monotherapy (8).

To our knowledge, our study is the first study in the literature which compares the toxicity and efficacy of FOLFIRINOX versus cisplatin–gemcitabine combination versus gemcitabine monotherapy schedules in elderly patients with PC. In the present study, cisplatin–gemcitabine combination showed a favourable outcome (17 months of m OS and 25% of DCR) compared with FOLFIRINOX (11 months of m OS and 6.2% of DCR) and gemcitabine monotherapy (8 months of m OS and 26.7% of DCR); however, the difference was not significant (p=0.164) by using the Kaplan–Meier method. But by using the Cox proportional hazards regression model, preformation of cisplatin–gemcitabine chemotherapy was predicted to have better overall survival with regard to FOLFIRINOX (HR: 0.213; 95% CI, 0.065–0.699, p=0.011).

Grade 3–4 neutropenia, Grade 3–4 FEN, Grade 3–4 thrombocytopenia and Grade 1–2 sensory neuropathy frequencies were unsignificantly increased but hospitalisations due to toxicities were significantly increased in the FOLFIRINOX treatment group. A retrospective single-centre trial reported FOLFIRINOX as a feasible regimen with comparable survival in PC and colorectal cancer patients aged 70 or above (21). However, it was also reported that 75% of patients had reduction in chemotherapy doses, 67% of patients experienced diarrhoea and 38.5% of patients had stopped treatment due to severe toxicities. The present study showed 11 months of m OS in FOLFIRINOX group, which is comparable with the previous studies, but increased febrile neutropenia, diarrhoea and sensory neuropathy has also been reported with the FOLFIRINOX group (9, 10, 15, 17, 21).

Guion-Dusserre et al. (21) reported none of the geriatric parameters (age, comorbidities, ECOG PS) were limiting factors for chemotherapy use and survival. In our study only PTR was associated with better PFS and only liver metastases was found to be associated with worsened OS. Von Hoff et al (10) reported more advanced disease with liver involvement and poor ECOG PS had greatest risk reduction in death with combination chemotherapy. They also showed longer treatment duration with increased cumulative dose, had better effect on OS like our study.

Retrospective nature of the study and low numbers of patients are the limitations of our study, resulting in possible selective bias and under-reporting of toxicity.

In conclusion, optimum first-line treatment in elderly patients with advanced PC is not yet been defined. To our knowledge, the present study is the first one in literature to compare FOLFIRINOX, cisplatin–gemcitabine and gemcitabine. The present study revealed that the cisplatin–gemcitabine combination schedule had an improved OS and reasonable toxicities for elderly patients with advanced PC.

CONFLICT OF INTEREST

None.

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