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FOLFIRINOX Rejimi Rezeke Edilmiş Pankreas Kanserinde Daha Mı Etkili ?

Is FOLFIRINOX Better In Primary Resected Metastatic Pancreatic Cancer ?

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Öz

Giriş ve Amaç: Pankreas kanseri çok ölümcül bir hastalık olup 2030 yılında ABD'de kanser ölümlerinde ikinci sırada olacağı tahmin edilmektedir. Kemoterapi genellikle metastatik pankreas duktal adenokarsinomunda en önemli tedavi seçeneğidir ve palyatif amaçlı uygulanmaktadır. Çok ilaçlı bir rejim olan FOLFIRINOX, desmoplastik özellikteki bu kanserde kemorezistansın üstesinden gelmek için iyi performans gösteren hastalarda önemli bir tedavi seçeneğidir. Pankreas kanserinde kemorezistansı ortadan kaldırmanın en önemli yolu cerrahidir. FOLFIRINOX, cerrahi uygulanabilen hastalarda dahi hastalık yeniden ortaya çıktığı ve gemsitabinden daha iyi sağkalım sonuçları verdiği için adjuvan tedavide kullanılmıştır. FOLFIRINOX rejimi ile, primer lezyona yönelik cerrahi olan ve sonrasında metastaz yapmış pankreas duktal adenokarsinomlu hastalarda, metastatik olarak prezente olmuş (de novo metastatik) hastalara gore daha iyi yanıt elde edilebildiğine dair veriler mevcuttur. Bu retrospektif çalışma, daha önce opere edilmiş ve metastaz geliştirmiş (cerrahi grubu) ve tanı anında metastatik hastalığı olanların (de novo metastatik grup) FOLFIRINOX rejimine verdikleri yanıtları araştırmak üzere planlanmıştır.

Gereç ve Yöntemler: 2013-2017 yılları arasında takip edilen 35 hasta çalışmaya dahil edilerek tıbbi kayıtları incelendi.

Bulgular: Cerrahi grubun progresyonsuz sağkalımı medyan 10 aydı. De novo metastatik grupta progresyonsuz sağkalım medyan 6 aydı (tablo 2). Cerrahi grupta progresyonsuz sağkalım de novo metastatik gruba göre istatistiksel olarak anlamlı uzundu (p: 0,033). Cerrahi grup genel sağkalım 20 ay iken de novo metastatik grup genel sağkalımı 7 aydı. Cerrahi grubun genel sağkalımı de novo metastatik gruba göre istatistiksel olarak anlamlı derecede daha uzundu (p: 0,020).

Sonuç: Çalışmamızın sonuçlarına göre FOLFIRINOX tedavisi, primer pankreas tümörü opere edilen ve ardından metastaz gelişen pankreas duktal adenokarsinomlu hastalarda daha etkilidir. Bu nedenle, performansa bakılmaksızın FOLFIRINOX uygulaması cerrahi yapılmış hastalarda uygun olabilir. Ayrıca hastalık yükünü azaltmak için opera edilen hastalarda daha iyi sonuçlar alınması nedeniyle, hastalık yükünü azaltmak için cerrahi tedaviler metastatik hastalarda uygulanabilir. Sonuçlarımızın valide edilebilmesi için daha geniş hasta popülasyonları ile randomize çalışmalar yapılmasına ihtiyaç bulunmaktadır.

Anahtar kelimeler: Cerrahi, FOLFIRINOX, Pankreas Kanseri.

Abstract

Objective: Pancreatic cancer is a very fatal disease and is estimated to be the second leading cause of cancer deaths in the USA in 2030. Chemotherapy is usually the most important treatment option in metastatic pancreatic ductal adenocarcinoma and is applied for palliative purposes. FOLFIRINOX, which is a multi-drug regimen, is an important treatment option in patients with good performance in order to overcome chemoresistance in this desmoplastic cancer. Surgery is the most important way to eliminate chemoresistance in pancreatic cancer. FOLFIRINOX is preferred in

adjuvant therapy because the disease reoccurs even in patients who can undergo surgery and it gives better survival results than gemcitabine. There is data suggesting that patients with pancreatic ductal adenocarcinoma who underwent surgery for the primary lesion and subsequently metastasized may have a better response with the FOLFIRINOX regimen than patients with metastatic presentation (de novo metastatic). This retrospective study was planned to investigate the response of previously operated patients who developed metastases (surgical group) and those with metastatic disease at the time of diagnosis (de novo metastatic group) to the FOLFIRINOX regimen.

Materials and Methods: 35 patients followed between 2013 and 2017 were included in the study and their medical records were examined.

Results: Progression free survival of surgery group was median 10 months. De novo metastatic group progression free survival was median 6 months (table 2). Surgery group progression free survival was statistically significant longer than de novo metastatic group (p:0.033). Surgery group overall survival was 20 months. De novo metastatic group overall survival was 7 months. Surgery group overall survival was statistically significant longer than de novo metastatic group (p:0.020).

Conclusion: According to the results of our study, FOLFIRINOX treatment is more effective in patients with pancreatic ductal adenocarcinoma who underwent surgery for a primary pancreatic tumor and then developed metastasis. Therefore, regardless of performance, administration of FOLFIRINOX may be appropriate in patients who have undergone surgery. In addition, surgical treatments can be applied to metastatic patients to reduce the disease burden, since better results are obtained in patients who have been operated for palliative purposes. Randomized studies with larger patient populations are needed to validate our results.

Keywords: Pancreatic Cancer, FOLFIRINOX, Surgery.

1. Introduction

Pancreatic cancer is a very fatal disease and is estimated to be second in cancer deaths in the USA in 2030 [1]. Again in the USA, approximately 57000 patients are diagnosed with pancreatic cancer annually and almost all of them are expected to die due to this disease [2]. Pathology of patients with this diagnosis is about 85% adenocarcinoma arising from ductal epithelium. The only chance of cure in these patients is surgery, but a small portion of patients (15-20%) are potentially candidates for surgery at the time of diagnosis. The 5-year survival rate is around 10% even in patients who can be operated [3,4]. Despite adjuvant therapy, the majority of patients (69-75%) develop recurrence within 2 years [5-7].

Chemotherapy is usually the most important treatment option in metastatic pancreatic ductal adenocarcinoma and is applied for palliative purposes. Overall survival is poor even in patients receiving chemotherapy. Single agent gemcitabine, gemcitabin plus nab-paclitaxel and FOLFIRINOX regimens were used in patients with metastatic ductal pancreatic adenocarcinoma and survival data were 6 months, 8 months, 11 months, respectively [8,9]. The choice between these three regimens is determined by the patient's performance status. One of the most important reasons for the inadequacy of treatment in this disease with a low survival rate is the chemotherapy-resistant nature of pancreatic ductal adenocarcinoma. FOLFIRINOX, which is a multi-drug regimen, is an important treatment option in patients with good performance status in order to overcome chemoresistance in this desmoplastic cancer.

The desmoplastic structure of pancreatic ductal adenocarcinoma is thought to be responsible for the chemoresistance. Desmoplastic reaction in pancreatic cancer has a unique structure among solid tumors. Desmoplasia in this cancer consists of two components: cellular and non-cellular. The cellular component contains pancreatic stellate cells and immune cells [10,11]. In normal pancreas, these satellite cells are inactive cells with vitamin A droplets in their cytoplasm. They become active in pancreatic inflammation or damage and lose the vitamin A droplets in their cytoplasm. These cells, which have undergone molecular and functional changes, are thought to be the most important regulators in the formation of pancreatic cancer-related desmoplasia, cancer cells proliferation, metastasis and chemoresistance [12, 13]. Especially as a result of excessive extracellular matrix and accumulation of activated satellite cells, this high desmoplastic structure physically compresses the tumor vascular structure by forming a barrier. This results in a heterogeneous and weak tumor perfusion [14, 15]. These mechanical vascular barriers cause ineffectiveness of chemotherapeutics and poor prognosis [16-19].

The most important way to eliminate this chemoresistance is surgery. FOLFIRINOX is used in adjuvant therapy, as the disease largely recurs even in operated patients, and it gives better survival results than gemcitabine. [20]. Based on these results, the FOLFIRINOX regimen used to overcome chemoresistance may respond better than de novo metastatic pancreatic ductal adenocarcinoma in patients with metastasized pancreatic ductal adenocarcinoma. From this point of view, we planned this retrospective study to investigate the responses of patients who had previously been operated and developed metastases (surgery group) and those who had metastatic disease at the time of diagnosis (de novo metastatic group) to the FOLFIRINOX regimen.

2. Materials and ve Methods

This is a retrospective study performed in two different tertiary health institutions. It was based on routinely

collected data from charts of patients. Data of the patients who were followed up between 2013 and 2017 were collected. Inclusion criteria were ≥18 years old, pathologically confirmed pancreatic adenocarcinoma who has metastasized, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, received FOLFIRINOX for first line treatment. Patients may have received adjuvant treatment (radiotherapy, chemotherapy or chemoradiotherapy) for their disease. We retrospectively reviewed 35 patients. These patients with metastatic pancreatic adenocarcinoma were divided into two groups. The first group consists of patients who were previously operated for pancreatic cancer and metastases were detected during their follow-up (surgery group). There were 8 patients in surgery group. In the second group, patients who were metastatic at the time of diagnosis (de novo metastatic group) were examined. There were 27 patients in de novo metastatic group. The characteristics of these two groups were compared.

The primary endpoint of the study was progression-free survival. Progression-free survival was defined as the time from the first cycle of FOLFIRINOX treatment to the day progression was detected. The second endpoint was determined as overall survival. Overall survival was defined as the time from the first cycle of FOLFIRINOX treatment to death.

Data analysis was performed using the IBM SPSS Statistics (IBM Corp. Armonk, NY, USA) for Windows, version 20.0. Numerical variables were expressed as mean and standard deviation or median (minimum-maximum), where appropriate. General characteristics of subgroups were compared using a *Mann-Whitney U* test. The PFS and OS rates were estimated by the Kaplan-Meier method and compared with log-rank test. A p value of ≤0.05 was considered statistically significant. Study was reviewed by approval of the Local Ethics Committee.

3. Results and Discussion

3.1.Results

35 patients were enrolled between 2013-2017. Data lock was 10 October 2018. All patients were metastatic and received first line FOLFIRINOX. Median age of study population was 54. In the de novo metastatic group 21 patients were male, median age was 54, 12 patients had carcinoma of the head, 6 patients had carcinoma of body and 9 patients had carcinoma of tail, 4 patients had biliary stent. In the surgery group 6 patients were men, 2 patients were women, median age was 62.5. Seven out of eight patients had carcinoma of head and one of them was carcinoma of tail. Two patients had biliary stent (Table 1).

Table 1. Demografic and clinical characteristics of patients

	De novo metastatic group	**Surgery group**	**Total**
Male	21	6	27
Female	6	2	8
Age (range)	54 (44-71)	62,5(53-75)	54(44-75)
ECOG performance status 0	12	7	19
ECOG performance status 1	15	1	16
Carcinoma of head	12	7	19
Carcinoma of body	6	0	6
Carcinoma of tail	9	1	10
Biliary stent	4	2	6

Primary endpoint was progression free survival. Two patients in surgery group and 1 patient in de novo metastatic group did not progressed. Progression free survival was median 10 months in the surgery group and 6 months in the de novo metastatic group (Table 2).

Table 2. Progression Free Survival (months)

Group	Mean				Median			
	Estimate	Std.error	%95 confiden interval		Estimate	Std.error	%95 confidence interval	
			Lower bound	Upper bound			Lower bour	Upper bound
Surgery	6,407	,869	4,704	8,111	6,00	1,291	3,470	8,530
De novo	12,792	2,819	7,266	18,317	10,0	2,121	5,842	14,158
Overall	7,879	1,023	5,873	9,884	7,00	,976	5,087	8,913

Progression free survival of the surgery group was statistically significantly longer than the de novo metastatic group (p:0.033) (Table 3).
Secondary endpoint was overall survival. Three patients in surgery group and one patient in de novo metastatic group were alive. Overall survival was 20 months in the surgery group and 7 months in the de novo metastatic (Table 4).
Overall survival of the surgery group was statistically significantly longer than the de novo metastatic group (p:0.020) (Table 5).

Table 3. Progression Free Survival Log Rank

	Chi-Square	**df**	**Sig.**
Log Rank (Mantel-Cox)	4,570	1	,033
Breslow (Generalized Wilcoxon)	4,086	1	,043

Test of equality of survival distributions for thedifferent levels

Table 4. Overall Survival (months)

Groups	Mean				Median			
	Estimate	Std.error	%95 confidence interval		Estimate	Std.error	%95 confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Surgery	10,315	1,928	6,536	14,09	7,00	2,596	1,911	12,089
De novo	24,825	6,122	12,82	36,82	20,0	4,066	12,030	27,970
Overall	13,558	2,240	9,168	17,94	10,0	2,410	5,275	14,725

Table 5. Overall Survival Log Rank

	Chi-Square	**df**	**Sig.**
Log Rank (Mantel-Cox)	5,379	1	,020
Breslow (Generalized Wilcoxon)	4,951	1	,026

Test of equality of survival distributions for thedifferent levels

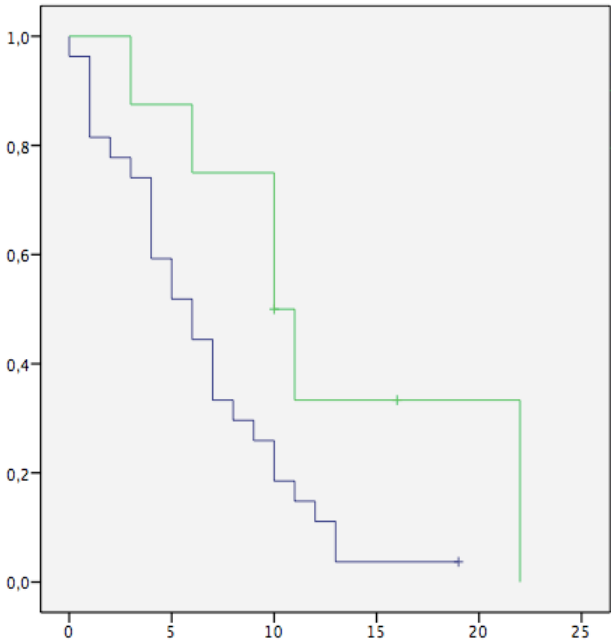


Figure 1. Progression Free survival (*Green curve: surgery group, blue curve de novo metastatic group.)

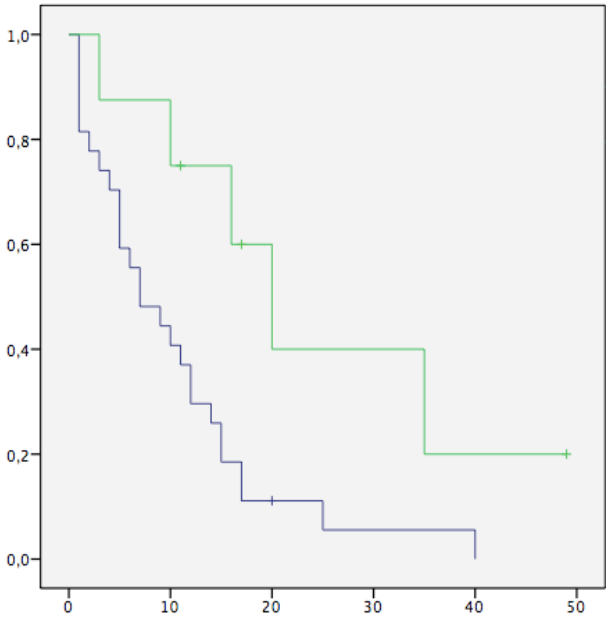


Figure 2. Overall Survival (*Green curve: surgery group, blue curve de novo metastatic group.)

3.2.Discussion

FOLFIRINOX is the first choice chemotherapy regimen worldwide in metastatic patients with good performance. The results of our study confirmed the fact that it gave better results especially in the group that had previously undergone primary surgery for its disease indicating that FOLFIRINOX should be used in this group regardless of performance. The study of Conroy at all using FOLFIRINOX as an adjuvant chemotherapy regimen supports this thesis [20]. According to this study, FOLFIRINOX showed better disease-free survival and overall survival in adjuvant therapy than gemcitabine. Although different patient groups were evaluated in these studies, FOLFIRINOX was more successful in patients undergoing primary pancreatic surgery. In our study, we tried to evaluate the efficacy of FOLFIRINOX in patients with previously operated for primary pancreatic cancer and non-operated (de novo) metastatic pancreatic ductal adenocarcinoma. In our patient population progression-free survival and overall survival were statistically different between the two groups. Median duration of progression-free survival was 10 months for surgery group, and 6 months for de novo metastatic group. Median duration of overall survival was 20 months in the surgery group, and 7 months in the de novo metastatic group.

In another study, which compared FOLFIRINOX and gemcitabine for the first-line treatment in metastatic pancreatic cancer, which was made by Conroy at all, the progression-free survival of the FOLFIRINOX group was found to be 6.8 months [21]. In our study, median progression-free survival of the de novo metastatic group was 6 months and this is similar to the pivotal study of FOLFIRINOX [21]. But overall survival was 11.3 months in the pivotal study of FOLFIRINOX and this period was 7 months in the de novo metastatic group in our study. This difference may have occurred due to the low number of patients and inadequate patient selection. However, overall survival was 20 months in our study in the previously operated group. According to the FOLFIRINOX pivotal study, overall survival duration was better.

The low number of patients is one of the limitations of our study. In addition, the surgical patient group and the de novo metastatic group may have different biological aspects. Therefore, having such a bias in patient selection is another limitation of our study in terms of obtaining objective results

There are many reasons why surgically treated patients respond better to chemotherapy. Considering the desmoplastic structure of pancreatic cancer and mechanical pressure on the vascular structure, the operation of the primary lesion may cause greater effect of chemotherapy. Based on this mechanism, reducing the burden of the disease by performing a kind of debulking surgery may also increase the effectiveness of chemotherapy. In other words, reducing tumor burden can prolong survival. It may be recommended to reduce the burden of disease by performing surgery in selected patients with good performance in the treatment course of metastatic pancreatic ductal adenocarcinoma. However, due to factors such as low number of patients and retrospective design of our study, larger-scale randomized controlled studies can be conducted to clarify this issue.

4. Conclusion

According to the results of our study, FOLFIRINOX treatment is more effective in patients with pancreatic ductal adenocarcinoma who underwent primary pancreatic tumor surgery and subsequently developed metastases. Therefore, treatment with FOLFIRINOX regardless of performance status may be appropriate in patients who have undergone surgery. In addition, due to the better results in patients who underwent surgery to reduce the burden of disease, it may be considered to design studies involving large patient populations to evaluate the results of adding palliative surgical interventions to the treatment of metastatic patients.

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