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Comparison of taxan-cisplatin combination with gemcitabine -cisplatin combination in metatastatic non-small cell lung cancer

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SUMMARY

In the first stage treatment of NSCLC, it is controversial which treatment combination should be preferred and advantage of one combination over the other could not be shown. The purpose of this study is to compare gemcitabine-cisplatin combination and taxan-cisplatin combination in phase 4 NSCLC with, in terms of efficacy, cost and toxicity. Patients whose diagnoses were phase 4 NSCLC in, Department of Medical Oncology between 2008-2011 have been collected. All diagnosis were confirmed histopathologically and radiologically shown to be metastatic. When two regimens were evaluated together, median survival of the patients was determined as 10,6 (95% confidence interval 5,4- 15,7) months. While survivel time was 8,1 months (%95 confidence interval 5,1- 11,27) for Gemzar-cisplatin regimen, it was 14 months (95% confidence interval 5,5- 22,5) in taxan-cisplatin regimen. But when the difference between survival times was evaluated with long rank test, statistically significant difference was not determined. We argue that, while choosing the combination thrapy in the first stage therapy of phase 4 NSCLC, besides the performance status of the patient and possible side effects, cost of the therapy should also be taken into consideration.

Key words: *Lung cancer, Gemsitabine, Taxans, Treatment*

ÖZET

Metastatik küçük hücre dışı akciğer kanserinde taxan-sisplatin mombinasyonu ile gemsitabin-sisplatin kombinasyonunun karşılaştırılması

Metastatik küçük hücre dışı akciğer kanserinde birinci basamak tedavide hangi tedavi kombinasyonunun tercih edilmesi gerektiği tartışmalıdır. Bu çalışmamızın amacı evre 4 KHDAK'de sık kullandığımız gemsitabin-cisplatin kombinasyonuna karşı taxan-sisplatin kombinasyonunun etkinlik toksite ve maliyetini karşılaştırmaktır. 2008-2011 yılları arasında Tıbbi Onkoloji kliniğinde histopatolojik olarak tanısı doğrulanmış ve görüntüleme yöntemleri ile metastatik olduğu gösterilmiş hastalar çalışmaya alınmıştır. Her iki tedavi rejimi birlikte değerlendirildiğinde hastaların medyan yaşam süresi 10,6 (%95 güven aralığı 5,4- 15,7) ay olarak tespit edildi. Gemzar-sisplatin kolunda bu süre 8,1 (%95 güven aralığı 5,1- 11,27) ay iken taksan-sisplatin kolunda 14 (%95 güven aralığı 5,5- 22,5) ay olarak tespit edildi. Yaşam süreleri arasındaki fark long rank testi ile değerlendirildiğinde istatiksel anlamlı fark tespit edilmedi. Evre 4 KHDAK ilk basamak tedavisinde kombinasyon seçiminde hastanın performans durumu, olası tedavi etkileri yanında tedavi maliyetinin de göz önünde bulundurulması gerektiğini düşünüyoruz.

Anahtar kelimeler: *Akciğer kanseri, Gemsitabin, Taksanlar, Kemoterapi*

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Introduction

In spite of a number of prevention studies, lung cancer continues to be the most frequently encountered cancer worldwide (1). Treatment of the patients with lung cancer depends on the cell type, tomor stage, molecular characteristics of the tumor such as EGFR, ALK expressions and overall performance of the patient (2).

In patients with phase 1-3 non-small cell lung cancer (NSCLC), curative surgery, radiotherapy and chemotherapy combination can be used. On the other hand, in stag4 patients, the purpose of the treatment is palliation. In the metastatic disease, anti-tumoral activities of cisplatin, gemcitabine and taxans (paclitaxel, docetaxel), when used as a single agent, have been demonstrated (3-6).

Combination of these agents has superior effects over single agent therapies in metastatic NSCLC and taxan-cisplatin, gemcitabine-cisplatin are the frequentlyused combinations (7-10). On the other hand, which combination should be choosen in the first step treatment of metastatic NSCLC.t is still debatable. There are conflicting data on this subject, it was not possible to show priority of the combinations over each other (11).

The purpose of this study is to compare gemcitabine-cisplatin combination and taxan-cisplatin combination in phase 4 NSCLC in terms of efficacy, cost and toxicity.

MATERIAL and METHODS

Patient Group

Patients whose were diagnosed phase 4 NSCLC in Antalya Education and Research Hospital, Department of Medical Oncology between 2008-2011 have been collected. All diagnoses were confirmed histopatho-

logically and radiologically shown to be metastatic. The patients with a performance score of ECOG 0-2, objectively measurable disease, sufficient bone marrow reserve and normal hepatic and renal functions have been involved in the study. Patients files have been retrospectively analysed and the information about the phase of the disease and treatments received have been obtained. Chemotherapy combination protocols administration every 21 days of the combination (consisted of Gemcitabine 1000 mg/m2 D1-8, Docetaxel 75 mg/m2 D1, Paclitaxel 175 mg/m2 D1 with cisplatin 75 mg/m2 D1) have been administered to the patients at least for one cycle. Body surface area was calculated with DuBois formula (BSA: (Weight 0,425 x Height 0,725)x0,007184). Those patients with 3 or higher ECOG score and those whose treatments have been initiated at a different medical center and continued in our clinic have been excluded from the study.

Statistical Analysis

Statistical analysis was performed with SPSS 15.0 software. Distribution of variables was analyzed by visual and analytical methods (Kolmogorov-Smirnov). Since two chemotherapy regimens, age, gender and the laboratory values at the beginning of chemotherapy were not demonstrating normal distribution, they were compared with Mann-Whitney U test. Effects on survival of the chemotherapy between different combinations have been examined with log-rank test. Survival rates have been calculated using Kaplan Meier survival analysis. The results with P value of less than 0,05 were evaluated as statistically significant.

RESULTS

Sixty patients were identified as eligible. There were 17 (28.3%) female and 43(71.7%) male . Median age of the patients were 58.5±11.3. Between two therapy regimens, no significant difference was found in terms of the initial laboratory values, age and gender distribution.

Most frequent application symptoms of patients were determined as cough (81.7%) and weight loss (51.7%). Most frequent site of metastasis was bone (40%). Other sites were pleura with malignant pleural effusion within 14 patients (23.3%) and liver within 6 patients (11.7%). No differences were determined between chemotherapy regimens in terms of metastasis site. (p:0.628) While most frequently encountered histological type was adenocarcinoma within 32 patients (53.3%), squamous cell carcinoma was determined as having the second highest frequency within 24 patients (40%). Patients recived median 3 chemotherapy cycles. Between two therapy regimens, there was no difference between the chemotherapy cycles administered. (p:0.776) While 8 patients took paclitaxel -cisplatin combination in taxan-cisplatin regimen, 17 took docetaxel-cisplatin chemotherapy combination. Average body surface area was found as 1,68. Cost of gemzar-cisplatin therapy administered 3 cycles for average body surface area was found as 3.246,66 TL. While the cost of paclitaxel-cisplatin combination was 2.905,92 TL, the cost of docetaxel cisplatin was found as 3.885,12 TL.

Side effects between therapy regimens were also studied. While nausea and vomiting were determined as the most frequent side effect in gemcitabine regimen, hematological toxicity was determined in chemotherapies with taxan (Table 1). In spite of the gemcitabine regimen, there was no hospitalization because of febrile neutropenia, 3 patients who received docetaxel and one patient who received paclitaxel were hospitalized because of febrile neutropenia.

When two regimens were evaluated together, median survival of the patients was determined as 10.6 (95% confidence interval 5.4- 15.7) months. While survivel time was 8.1 months (%95 confidence interval 5.1- 11.27) for Gemzar-cisplatin regimen, it

Table I. Side effects found in patients

		Gemsitabine-CDPP 35	*Dosetaxel-CDPP 17*	*Paklitaxel-CDPP 8*
Neutropenia	Grade 1-2	7 (%20)	4 (%23)	2(%25)
	Grade 3-4	1 (%2.8)	3 (%17.6)	1(%12,5)
Anemia	Grade 1-2	10(%28.5)	2 (%11.7)	1(%12,5)
	Grade 3-4	-	-	-
Thrombocytopenia	Grade 1-2	6 (%17.1)	1 (%5.8)	1(%12,5)
	Grade 3-4			
Nausea and Vomiting	Grade 1-2	31 (%88.5)	6 (%35)	3(%37.5)
	Grade 3-4	3(58.5)	1(%5.8)	-
Diarrhea	Grade 1-2	2 (%5.7)	2(%11.7)	1(%12,5)
	Grade 3-4	-	-	-
Neuropathy	Grade 1-2	1(%2.8)	3 (%17.6)	2(%25)
	Grade 3-4	-	-	-
Mucositis	Grade 1-2	5(%14.2)	2 (%11.7)	3(%37.5)
	Grade 3-4	-	-	-

was 14 months (95% confidence interval 5.5- 22.5) in taxan-cisplatin regimen. But when the difference between survival times was evaluated with long rank test, statistically significant difference was not determined. (Figure 1)

DISCUSSION

Our study revealed no significant difference in median survival between the regimen with gemcitabine and the regimen with taxan. Significant results were determined only with the side effects. When the combinations with taxan were evaluated in means of cost, the cost of paclitaxel combination was lower than other two combinations.

Schiller et.al. have studied the efficiencies of using the combination of cisplatine with gemcitabine, paclitaxel and docetaxel and the carboplatin paclitaxel combination on local advanced phase and metastatic patients in their ECOG 1594 study. In this study, where median survival was determined as 7.9 months, no difference with respect to survival durations was determined among four chemotherapy regimens. In our study, median survival was determined as 10.6 months (11).

In a study where paclitaxel-carboplatin, gemcitabine-cisplatin, vinorelbin-cisplatin are compared, median survivals have been determined as 9.9, 9.8 and 9.5 months respectively. Among treatment regimens, no difference in terms of median survival, response rates have been determined. It was demonstrated that side effects were mostly seen in vinorelbine cisplatin regimen, which is the standard regimen, and that the average number of chemotherapy cycle given was less than others (12).

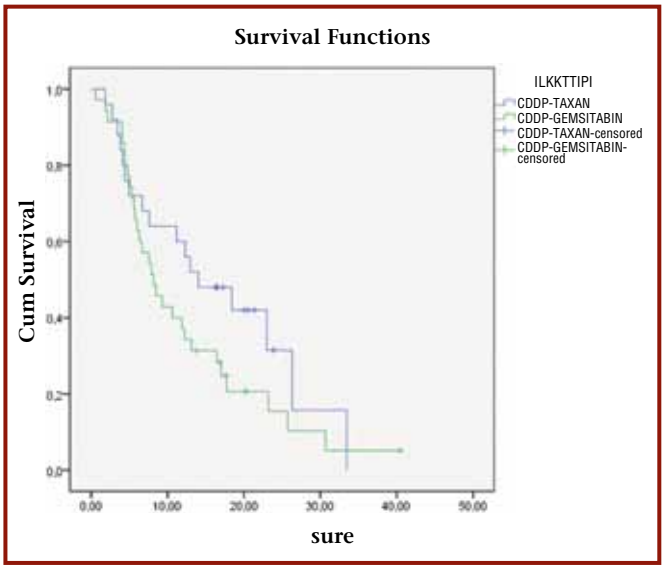

Figure 1. Survival in both treatment arms graphic

In a study conducted with Japanese patients, efficacy of irinotecan Cisplatin-irinotecan, Carboplatin-paclitaxel, Cisplatin-gemcitabine, Cisplatin -vinorelbine on phase 3b and phase 4 patients has been investigated. No difference in terms of median survival and response rate have been determined between therapy regimens. Median survivals similar to our study have been determined 13.9, 12.3, 14.0 and 11.4 months respectively (13). Efficacy of taxans depend on the ethnic groups. For example, CYP3A gene polymorphism can change docetaxel pharmacokinetics. Goh et.al. have demonstrated in their study that CYP3A activity is lower in Asia-based people (14). These personal and ethnical differences may be the reason for differences in therapy responses and toxicity.

In EORTC 08975 study, gemcitabine-cisplatin, paclitaxel-cisplatin and gemcitabine-paclitaxel regimens have been compared. While significant difference between median survivals was not found, it was determined that the cost of gemcitabine-paclitaxel combination was higher (15). Similar studies have compared the combination of gemcitabine with carboplatin and paclitaxel with paclitaxel carboplatin combination and no difference with respect to median survival has been determined (16-19).

Current therapy decision in NSCLC is relied on histological subtypes of tumor, precense of molecular markers such as EGFR mutation and ALK fusion oncogene on tumor tissue. If molecular markers are negative, cytotoxic chemotherapy combinations are used in first stage therapy (20). Consistent with the literature, it was demonstrated in our study that the chemotherapy combinations containing cisplatin based taxan or gemcitabine were not different in terms of median survivals. For this reason, we argue that, while choosing the combination thrapy in the first stage therapy of phase 4 NSCLC, besides the performance status of the patient and possible side effects, cost of the therapy should also be taken into consideration.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59: 225.
2. Kulesza P, Ramchandran K, Patel JD. Emerging concepts in the pathology and molecular biology of advanced non-small cell lung cancer. Am J Clin Pathol. 2011;136: 228-38.

3. Bunn PA Jr. The expanding role of cisplatin in the treatment of non-small-cell lung cancer. Semin Oncol 1989; 16: 10.
4. Ranson M, Davidson N, Nicolson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 2000; 92: 1074.
4. Roszkowski K, Pluzanska A, Krzakowski M, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). Lung Cancer 2000; 27: 145.
5. Gatzemeier U, Shepherd FA, Le Chevalier T, et al. Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study. Eur J Cancer 1996; 32A: 243.
6. Kaya AO, Buyukberber S, Dane F, et al.; Anatolian Society of Medical Oncology. Cisplatin plus docetaxel combination in the first-line treatment of metastatic non-small cell lung cancer. Tumori. 2010; 96: 400-404.
7. Yumuk PF, Turhal NS, Gumus M, et al. Results of paclitaxel (day 1 and 8) and carboplatin given on every three weeks in advanced (stage III-IV) non-small cell lung cancer. BMC Cancer. 2005; 25: 5-10.
8. Helbekkmo N, Sundstrøm SH, Aasebø U, et al. Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. Br J Cancer 2007; 97: 283.
9. Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Ann Oncol 2010; 21: 540.
10. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92.
11. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002; 20: 4285.
12. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007; 18: 317.
13. Goh BC, Lee SC, Wang LZ, et al. Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in Asians through phenotyping and genotyping strategies. J Clin Oncol 2002; 20: 3683-90.
14. Smit EF, van Meerbeeck JPAM, Lianes P et al. Three-arm randomized study of two cisplatin-based regimen and paclitaxel plus gemcitabine in advanced non-small cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group—EORTC 08975. J Clin Oncol 2003; 31: 3909-3917.
15. Treat JA, Gonin R, Socinski MA, et al. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Ann Oncol. 2010; 21: 540-7.
16. Gillenwater HH, Rowland KM, Comis RL, Obasaju CK, Belani CP. A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Lung Cancer. 2010; 70: 340-346 .
17. Treat J, Edelman MJ, Belani CP, et al.; Alpha Oncology Research Network. A retrospective analysis of outcomes across histological subgroups in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. Lung. 2010; 188: 359-64.
18. Li C, Sun Y, Pan Y, Wang Q, Yang S, Chen H. Gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel iadvanced non-small-cell lung cancer: a literature-based meta-analysis. Lung. 2010; 188: 359-64.
19. NCCN: Clinical Practice Guidelines in Oncology: V.12012.