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Original scientific paper

Gemcitabine in the First and Second-Line Chemotherapy of Advanced Non-Small Cell Lung Cancer

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A B S T R A C T

Aim of this study was to estimate efficacy of gemcitabine in first and the second-line chemotherapy for patients with advanced non-small cell lung cancer (stage III and IV). In first-line chemotherapy, 120 patients were treated with different chemotherapy regimens. Fifty-nine patients were treated with gemcitabine/cisplatin (PG), 41 with cisplatin/etoposide (PE) and 20 with mitomycin/ifosfamide/cisplatin (MIC). Forty patients, unsuccessfully treated with PE and MIC in first-line therapy were treated with PG (24 pts) and with best supportive care (BSC) (16 pts). In first-line therapy PG was superior to PE and MIC protocol (mean survival (MS) 10 vs. 7 vs. 8.5 months). Response rate (RR) for PG in first-line therapy was 46% and 21% in second-line. We showed also significantly better survival in patients treated with PG in second-line chemotherapy comparing to best supportive care (MS 9 vs. 5.5 months). Toxic side effects for combination PG was acceptable. This study confirmed that PG combination is safe and effective as first and second-line chemotherapy for patients with advanced non-small cell lung cancer.

Key words: *gemcitabine, lung cancer, NSCLC, chemotherapy*

Introduction

Lung cancer is a leading cause of death out of all carcinomas in the world. Non-small cell carcinoma (NSCLC) presents 80% of all cases of lung cancers[1]. At the time of diagnosis, majority of patients have locally advanced or metastatic disease (stages III B and IV). At the moment of diagnosis only third of patients are candidates for radical surgery. However, more than 50% of patients who underwent radical surgery will have relapse of cancer[2]. Summarizing these data, around 80% of patients with lung cancer are candidates for chemotherapy. A large number of patients on one hand and poor survival rate of patients on chemotherapy on the other hand make chemotherapy of small cell lung cancer very challenging. Because of that, many basic investigations and clinical studies have been conducted, including studies of new, third-line drugs for chemotherapy. Platinum based protocols are used for years showing a significant advantage in survival as compared with best supportive care[3]. According to meta-analysis, platinum based protocols decreased mortality by 27%, increased 1-year survival time by 10%, and increased survival for two months as compared with best supportive care. However, an average survival reached a Plato, and rarely exceeds 10 months. Majority of patients die within two years after diagnosis[4–7]. In the past ten years, many new drugs in different classes have been discovered and introduced to the clinical practice. For most of them, like paclitaxel, docetaxel, vinorelbine and gemcitabine, intensive clinical trials have been done. Our studies showed that those drugs were more effective in combination than as a monotherapy. With combination therapy response rate increased two times, survival time was longer for 2 months and one-year survival increased by 5%[8–9]. Most of the new drugs were also investigated in second-line chemotherapy in patients with no response to first-line chemotherapy and in patients with a relapse of cancer after first-line chemotherapy[10,11].

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Gemcitabine is analogous to nucleoside (2',2'-difuorodeoxycytidine), which stops DNA transcription and synthesis by implanting itself in DNA double helix[12]. Gemcitabine can be used as a monotherapy in treatment of NSCLC, but more often it is used in combination with cisplatin or carboplatin, due to synergistic effects of these two drugs[13].

The aim of this study was to estimate efficacy of gemcitabine in combination with cisplatin in first and second-line chemotherapy in Croatian patients with advanced non-small cell lung cancer (stages III A-N2, III B and IV).

Patients and Methods

We retrospectively analysed 120 patients (84 male and 36 female) treated at the University Hospital for Lung Diseases »Jordanovac« with gemcitabine in first and second-line chemotherapy during 2001 and 2002. Patients was classified according to cytological tumor type to: adenocarcinoma (73 pts), squamous cell carcinoma (planocellular carcinoma) (20 pts), large-cell carcinoma (7 pts), adeno-planocellular carcinoma (11 pts), non-differentiated carcinoma (9 pts); as stage IIIA-N2 (16 pts), stage IIIB (57 pts), stage IV (47 pts) and with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (21 pts), 1 (62 pts) and 2 (37 pts). We compared results of gemcitabine in combination with cisplatin (59 pts) with standard chemotherapy protocols usually used in the first-line chemotherapy in our hospital. Standard chemotherapy protocols include combination of cisplatin and etoposide (PE protocol) (41 pts) and combination of mitomycin, ifosfamide and cisplatin (MIC protocol) (20 pts). All patients unsuccessfully treated with PE and MIC protocols in first line (40 pts) were candidates for second line chemotherapy with gemcitabine. Efficacy and safety of gemcitabine and cisplatin in second line chemotherapy were analysed in group of patients who accepted second line chemotherapy (24 pts) and compared with patients treated only with best supportive care who refused this chemotherapy (16 pts).

Efficacy of chemotherapy was estimated by determine the percentage of patients with complete response (CR): disappearance of all tumor lesions, partial response (PR): regression more then 50% of tumor lesions, stable disease (SD): regression less then 50% or without progression of tumor lesions and disease progression (PD): progression during chemotherapy. We also analysed time to progression of disease (TTP): interval from the initiation of chemotherapy to disease progression, mean survival, and percentage of patients with one and two year survival. Toxicities were assessed at the end of every cycle using Worl Health Organisation (WHO) recommendations for grading of acute and subacute toxicity (grade 0–4).

Survival curves were calculated according to the method of Kaplan and Meier. Statistical probability (p-value) was calculated using Gehan-Wilcox test[14].

Chemotherapy protocols and dosage used in this study: 1. PE protocol: cisplatin 80 mg/m^2 on day 1 and etoposide 120 mg/m^2 on day 1, and 100 mg/m^2 on days 2 and 3; 2. MIC protocol: mitomycin 6 mg/m^2 and ifosfamide 3 g/m^2 and cisplatin 70 mg/m^2; 3. PG protocol: cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on day 1 and 8.

All protocols were applied every three weeks with an average number of cycles four.

Results

Our study included a total of 120 patients (84 males and 36 females), with an average age of 59 years (range from 41 to 78 years) and with cytological proven non-small cell lung carcinoma that were treated by chemotherapy. Most of the patients had adenocarcinoma (73 pts – 60%). Majority of patients were classified as stages III B and IV (104 pts – 87%) and only 16 patients – 13% were in stage III A-N2. A criterion for inclusion was ECOG performance status 0, 1 and 2. Of all analysed patients 59 were treated with gemcitabine and cisplatin, 41 with PE protocol and 20 patients with MIC protocol as first line chemotherapy. In 40 out of 61 patients, who were treated with standard protocols (PE and MIC protocols), there was a poor response. In 24 patients with poor response, second-line chemotherapy was applied according to gemcitabine and cisplatin protocol. Other 16 patients with poor response were treated with best supportive care (BSC) because they refused chemotherapy. In total, 12 patients were lost in the follow up (Table 1).

TABLE 1
PATIENTS' CHARACTERISTICS

	1-line total	PG 1-line	PE 1-line	MIC 1-line	PG 2-line	BSC
Sex						
Male	84	41	29	14	15	11
Female	36	18	12	6	9	5
Cytological tumor type						
Adeno	73	35	20	18	7	8
Plano	20	9	9	2	9	2
Macro	7	5	2	0	1	2
Adeno-plano	11	6	5	0	2	3
Nondifferentiated	9	4	5	0	5	1
Stage						
IIIA-N2	16	8	3	5	2	0
IIIB	57	28	14	15	18	2
IV	47	23	24	0	4	14
Performance status						
0	21	10	5	6	9	0
1	62	31	19	12	13	3
2	37	18	17	2	2	13

PG – cisplatin + gemcitabine, PE – cisplatin + etoposide, MIC – mitomycin + ifosfamide + cisplatin

TABLE 2
SUCCESS OF CHEMOTHERAPY

Response	PG 1st line	PE	MIC	PG 2nd line	BSC in 2nd line
CR	3 (5%)	0	1 (5%)	0	
PR	24 (40%)	5 (12%)	4 (20%)	5 (21%)	NA
RR (CR+PR)	27 (46%)	5 (12%)	5 (25%)	5 (21%)	
SD	28 (47%)	10 (24%)	5 (25%)	16 (67%)	
PD	4 (7%)	26 (64%)	10 (50%)	3 (12%)	
TTPD (median, range)	6 months (2–19)	4 months (2–8)	5 months (2–9)	5 months (3–9)	3 months (2–5)
MS (median, range)	10 months (3–25)	7 months (2–17)	8.5 months (6–17)	9 months (5–17)	5.5 months (4–12)

PG – cisplatin + gemcitabine, PE – cisplatin + etopiside, MIC – mitomycin + ifosfamide + cisplatin, CR – complete response, PR – partial response, RR – response rate, MR – minimum response, SB – stable disease, PD – disease progression, TTPD – time to disease progression, MS – mean survival, NA – not applicable

TABLE 3
TOXIC SIDE EFFECTS OF 3rd AND 4th DEGREE (ITS CLASSIFICATION) FOR CISTPALTIN/GEMCITABINE PROTOCOL

	PG	PE	MIC
Neutropenia	22 (27%)	14 (34%)	8 (40%)
Thrombocytopenia	21 (35%)	7 (17%)	3 (15%)
Nausea and vomiting	17 (21%)	7 (17%)	3 (15%)
Alopecia	8 (13%)	16 (39%)	8 (40%)
Changes on skin	1 (1%)	0 (0%)	0 (0%)
Neurological	1 (1%)	2 (5%)	1 (5%)

PG – cisplatin + gemcitabine, PE – cisplatin + etoposide, MIC – mitomycin + ifosfamide + cisplatin

In first-line chemotherapy, response rate was significantly better in patients treated with PG protocol when compared with PE and MIC protocol, 46% vs. 12% and 25% respectively. Median survival also proved to be better in patients treated with PG protocol than in patients treated with PE and MIC protocol, 10 month vs. 7 and 8.5 months. One-year survival was significantly better in patients treated with PG protocol than in patients treated with PE and MIC protocol, 37% vs. 23% and 30%. Two-year survival was 7% in patients treated with PG protocol. No patients treated with standard protocols survived 2 years. One year-survival in patients treated with PG protocol as second-line chemotherapy was 17%. These were patients who were treated with standard protocols (PE and MIC protocols) in first--line chemotherapy. Median survival of patients treated with PG protocol as second-line chemotherapy was 9 months vs. 5.5 months in group of patients treated only with best supportive care (Table 2).

The overall toxicity profile for all combinations of drugs was similar. PG produced less grade 3 and 4 alopecia and neutropenia but more grade 3 and 4 thrombocytopenia than did PE and MIC. Nausea and vomiting were reported more frequently in the gemcitabine arm than in PE and MIC (Table 3). Changes of skin and neurological toxicity were not significant in any schedule.

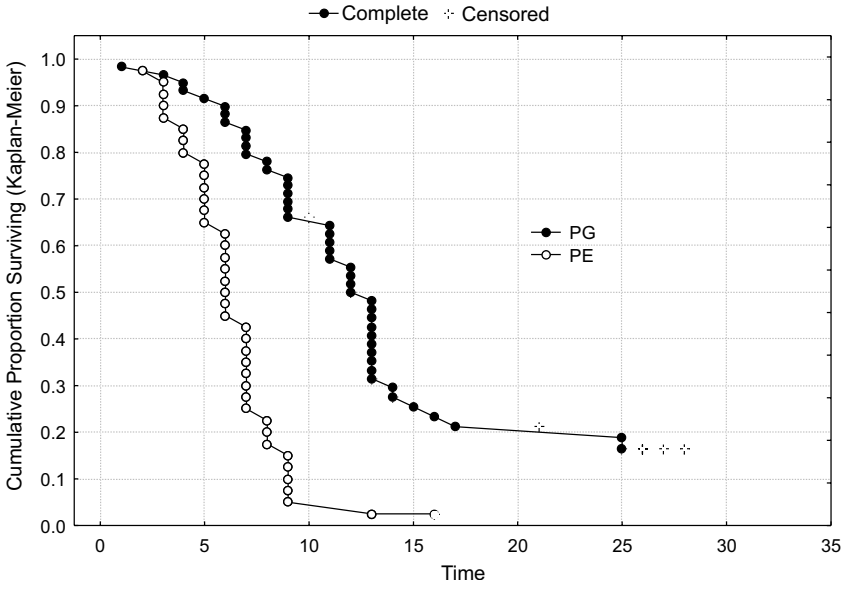

Fig. 1. Survival curves of patients treated in first-line chemotherapy with PG and PE: PG – gemcitabine/cisplatin, PE – cisplatin/etoposide.

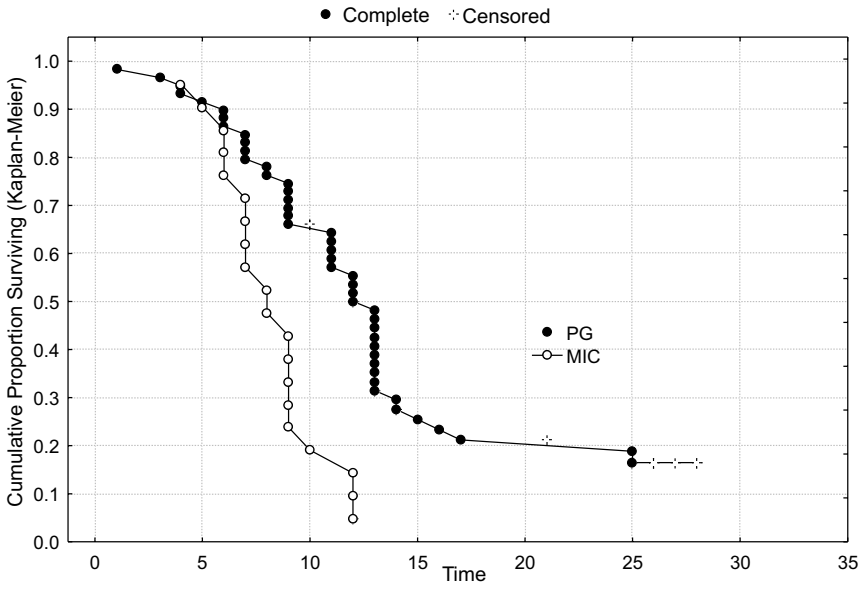

Fig. 2. Survival curves of patients treated in the first-line chemotherapy with PG and MIC: PG – gemcitabine/cisplatin, MIC – mitomycin/ifosfamid/cisplatin.

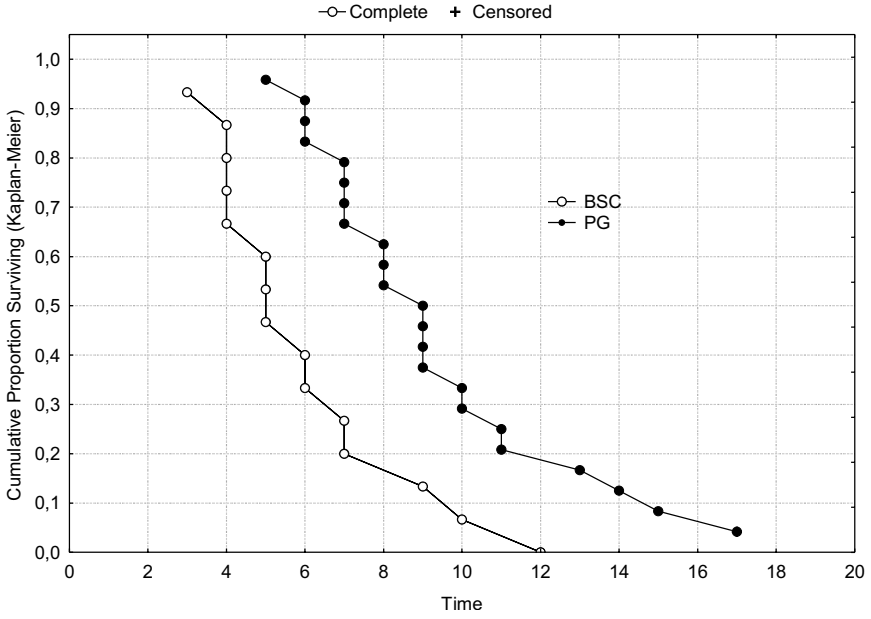

Fig. 3. Survival curves of patients treated in the second-line therapy with PG and BSC: PG – gemcitabine/cisplatin, BSC – best supportive care.

PG schedule offers a slightly better survival compared to standard chemotherapy setting (PE and MIC protocols) in first-line chemotherapy (Figures 1 and 2) and compared to BSC in second line setting (Figure 3).

Discussion

Results of this study showed that combination of cisplatin and gemcitabine is superior to standard protocols (PE and MIC protocols) in first-line chemotherapy of advanced non-small cell lung cancer. Many studies have compared cisplatin and gemcitabine with other standard protocols for first-line chemotherapy. Differences in the results of these studies can be explained by different inclusion criteria and different parameters used to estimate treatment efficacy. Cardenal et al[15] found no statistically significant difference in mean survival in patients treated with cisplatin and gemcitabine as compared to the patients treated with cisplatin and etoposide (8.7 vs. 7.2 months). In a large study by ECOG

1954, various combinations of platinum based drugs with paclitaxel, docetaxel and gemcitabine were compared. The results of that study showed no significant difference in survival, which was approximately 8 months[16]. Phase III study was conducted in 372 patients with stages III and IV non-small cell lung cancer who were not previously treated. It showed no benefit of carboplatin and gemcitabine as compared with combinations of mitomycin, ifosfamide and cisplatin and mitomycin, vinblastin and cisplatin. Mean survival was little over 7 months[17]. However, some studies showed significant benefit of cisplatin and gemcitabine in patients with advanced NSCLC as compared to standard protocols[18]. Crino et al. showed that patients treated with cisplatin and gemcitabine had response rate of 40.6% with mean survival of 13.5 months[19]. Our patients treated with combination of cisplatin and gemcitabine had response rate of 45% and mean survival of 10 months. Our results are in the middle of those two groups of studies which compared cisplatin and gemcitabin with other protocols. We showed a statistically significant improvement in survival (p=0.064) in the patients treated with PG protocol as compared with patients treated with PE and MIC protocols. Analyzing Kaplan-Meier's curve, we showed the greatest difference in survival. Survival was longer for more than 7 months in patients treated with PG protocol. Our results are in favor of study of Le Chevalier et al. which showed reduction of mortality by 3.9% per year in patients treated with gemcitabine based protocols as compared with non-gemcitabine protocols[20].

Our analysis of various agents in second-line chemotherapy showed that the best results were obtained in patients treated with docetaxel in second-line chemotherapy, for those patients who had a poor response on first-line chemotherapy, and in patients with relapse of disease after successful first-line chemotherapy. Docetaxel, as monotherapy in second–line chemotherapy in patients with unsuccessful first–line chemotherapy improved survival to 7.5 months with 1-year survival by 37%. These results are significantly better than in patients treated with best supportive care or combination of vinorelbine and ifosfamide[21]. Wachters et al. showed similar results in patients treated with docetaxel and carboplatin in second-line chemotherapy of advanced NSCLC[22]. Based on mentioned studies docetaxel is standard for second-line chemotherapy of advanced NSCLC.

Investigations on gemcitabine in second-line chemotherapy of advanced NSCLC are rare although the first results of its application in second-line therapy turned to be promising[23]. Studies of gemcitabine as second-line agent showed a significant efficacy with reasonable toxicity. Studies showed that patients with stages III and IV NSCLS treated with gemcitabine monotherapy in second-line chemotherapy had response rate approximately 20% with mean survival of 7 months and 1-year survival by 22%[24–26]. Combinations of gemcitabine with new generation of drugs showed better results than gemcitabine alone. Gemcitabine in combination with irinotecan had mean survival of 8.1 months with 1-year survival by 36%[27]. Combination with gemcitabine shoved similar results (8.3 months and 34.3%)[28]. Best results are achieved with combination of gemcitabine and docetaxel (mean survival of 11.1 months, and response rate of 41%) with mild toxic, mostly hematological side-effects[29]. In our study, the patients treated with cisplatin and gemcitabine combination in second-line chemotherapy had median survival of 9 month and with response rate of 17%. These results are similar to gemcitabine and irinotecan or vinorelbine combination. Comparing our results with results of studies of gemcitabine and docetaxel combination, we can conclude that combination of gemcitabine and docetaxel is superior to cisplatin and docetaxel in second-line chemotherapy. Toxic side-effects were similar in all studies.

This study confirmed that cisplatin and gemcitabine combination is safe and effective combination for treating patients with advanced non-small cell lung cancer in first as well in second line-chemotherapy. Our results are similar to the results of other studies which suggest that gemcitabine with cisplatin or carboplatin is one of the referential standards for treatment of advanced non-small cell lung cancer. Although there are no studies that compared gemcitabine and docetaxel in second-line chemotherapy, first results showed efficacy of gemcitabine, alone or in combination, as acceptable choice for second-line chemotherapy of advanced non-small cell lung cancer[30,31]. Our results confirm these conclusions. Limitation of our study is that is retrospective and on relatively small number of patients. Prospective studies have possibility for inclusion of more patients which can be randomly chosen. The use of more exact methods for diagnosing NSCLC will also contribute to better validation of chemotherapy results[32].

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GEMCITABINE U PRVOJ I DRUGOJ LINIJI KEMOTERAPIJE UZNAPREDOVALOG NEMIKROCELULARNOG KARCINOMA PLUĆA

S A Ž E T A K

Cilj sudije je bila procjena učinkovitosti gemcitabina u prvoj i drugoj liniji kemoterapije uznapredovalog nemikrocelularnog karcinoma pluća (stadij III i IV). Različitim kemoterapijskim protokolima liječeno je u prvoj liniji 120 bolesnika. Kod 59 bolesnika primjenjena je kombinacija gemcitabine/cisplatin (PG), kod 41 cisplatin/etoposide (PE) i kod 20 mitomycin/ifosfamide/cisplatin (MIC). Od četrdeset bolesnika neuspješno liječenih kombinacijama PE i MIC u prvoj liniji, njih 24 liječeno je u drugoj liniji kombinacijom PG, a 16 bolesnika samo suportivnom terapijom (BSC). U prvoj liniji kemoterapije PG protokol je pokazao bolje rezultate nego PE i MIC protokoli (srednje preživljenje (MS) 10 u odnosu na 7 i 8.5 mjeseci). Stopa odgovora (RR) za PG u prvoj liniji je bila 46% a u drugoj liniji 21%. Dokazali smo također da je preživljenje bolesnika liječenih kombinacijom PG u drugoj liniji znatno bolje, nego onih koji su lječeni samo suportivnom terapijom (MS: 9 u odnosu na 5.5 mj.). Nuspojave kod bolesnika liječenih kombinacijom PG su prihvatljive. Ovaj je rad pokazao da je gemcitabine (u kombinaciji s cisplatinom) siguran i učinkovit u prvoj i drugoj liniji kemoterapije uznapredovalog nemikrocelularnog karcinoma pluća.