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ORIGINAL ARTICLE

Important prognostic factors for the long-term survival in non-small cell lung cancer patients treated with combination of chemotherapy and conformal radiotherapy

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Summary

Purpose: *Combined modality therapy is standard of care for patients with unresectable locally advanced non-small cell lung cancer (NSCLC), however, insufficient data exist regarding prognostic factors in this disease setting.*

Methods: *To evaluate the treatment results and prognostic variables, 85 NSCLC patients treated from October 2005 to April 2008 were randomly assigned to one of the two treatment arms. In the first arm (sequential arm), 45 patients received sequential chemotherapy with 4 cycles of carboplatin and etoposide followed by conformal 3-dimensional (3D) radiotherapy (RT). In the second arm (concurrent arm), 40 patients received concomitant chemotherapy with cisplatin and etoposide and conformal RT, followed by two cycles of consolidation chemotherapy with carboplatin and etoposide.*

Results: *The median survival was 13 months for the patients in the sequential arm and 19 months for those in the concurrent treatment arm (p=0.0039). The disease-free survival (DFS) was 9 months in the sequential arm and 16 months in the concurrent treatment arm (p=0.0023). The following prognostic factors significantly influenced the survival of the patients treated with combination of RT and chemotherapy: age (p<0.05), performance status (PS) (p<0.001), weight loss (p<0.001), tumor size (p<0.05), nodal involvement (p<0.05).*

Conclusions: *Given the higher toxicity in the second arm, this should be reserved for younger patients (<70 years), having good PS and minimal weight loss. We highly recommend precise stage and prognostic factors definitions in such patients so that they receive the most beneficial treatment.*

Key words: *conformal radiotherapy, concurrent chemoradiotherapy, performance status, prognostic factors, stage, sequential chemoradiotherapy*

Introduction

Lung cancer remains a worldwide epidemic. Approximately 1.2 million people die from lung cancer each year. NSCLC represents over 80% of all lung cancers and 60-70% of the patients with NSCLC suffer from stage III or IV disease. In the late 1980s, RT was the standard treatment for these patients [1]. Later, randomized trials showed that chemoradiotherapy was superior to RT alone [2,3]. Many chemotherapeutic agents active in NSCLC possess radiosensitizing properties, thereby improving the probability of local control. In addition, chemotherapy administered concurrently with thoracic radiation may act systemically and potentially eradicate distant micrometastases. Several studies showed the feasibility of the cisplatin-etoposide combination plus RT for patients with stage III disease [4].

Successfully tailored therapy in lung cancer patients requires the definition of the prognostic factors. Prognostic factors are defined as characteristics of patients and stage before starting treatment. Analyzing these characteristics provides the opportunity to select patients in different groups and choose the best treatment modali-

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ty for the selected group. They are also important to evaluate the results of treatments and to compare the results of different clinical studies [5].

The primary end point of this study was to evaluate the treatment results and the prognostic variables in our patient population treated with sequential or concurrent chemoradiotherapy.

Methods

In this study 110 patients with NSCLC treated/followed-up from October 2005 to April 2008 at the University Clinic of Radiotherapy and Oncology in Skopje were analyzed. Only 85 patients (77%) were eligible for this study, aged between 18 and 70 years, with an Eastern Cooperative Oncology Group (ECOG) PS of ≤ 1 (range 0-1), and having ≤ 10% weight loss 3 months before study inclusion. All of them were previously untreated, had histologically or cytologically proven NSCLC, and unresectable stage IIIA-N2 disease, or stage IIIB disease without pleural effusion. Stage IIIB disease was assigned either by N3 (contralateral mediastinal or supraclavicular nodes) or by T4 from invasion of mediastinal structures.

The following prognostic factors were evaluated: age groups (18-43, 44-55, 56-70 years); histological type (squamous, adenocarcinoma, large cell carcinoma and unspecified type); ECOG PS, weight loss 3 months before inclusion (<5%, 5-10%); lymph node involvement; and tumor dimension (≤5 cm, >5 cm, and undetermined because of atelectasis, pneumonitis); symptom duration before treatment (<3 months, 3-6 months, >6 months); and hemoglobin level (<12 g/dl, ≥ 12 g/dl).

The following laboratory values were required: leucocytes ≥ $1.5x10^3$/l, platelets ≥ $100x10^3$/l, AST and ALT ≤ 2 the upper limit of normal. Exclusion criteria were as follows: uncontrolled infection or fever over 38 °C, unstable cardiovascular disease and previous malignancy. Before enrollment, the patients gave their full medical history and underwent clinical examination with assessment of PS.

Study arms

Patients were randomly assigned to receive sequential or concurrent therapy. In the sequential arm, 45 patients received 4 cycles of chemotherapy consisting of carboplatin (AUCx6) on day 1 and etoposide 100 mg/m^2/day on days 1-3, repeated every 3 weeks. RT began 4 weeks after the 4th cycle of chemotherapy administration. In the concurrent arm (40 patients), chemotherapy and RT began simultaneously. The RT schedule was identical to that in the sequential arm. The first cycle with cisplatin 30 mg/m^2 and etoposide 100mg/m^2 was administered on days 1 to 3 and the second 3-day cycle was administered in the last 3 days of RT. After 4 weeks of concurrent chemoradiotherapy, 2 cycles of consolidation chemotherapy were administered, consisting of carboplatin (AUC x 6) and etoposide 100 mg/m^2 on days 1 to 3.

Radiotherapy

Conformal RT in both arms consisted of 60 Gy in 30 fractions of 2 Gy per fraction, for 5 days a week given over a period of 6 weeks. Treatment planning CT was required to define the gross tumor volume (GTV). Each patient was positioned in an immobilization device-wing board in the treatment position on a flat table. CT slices with 5 mm thickness were obtained, starting from the cricoid cartilage and extending inferiorly to the level of the L1 vertebral body. The GTV, clinical target volume (CTV), planning target volume (PTV) and normal organs were outlined on all CT slices. The normal tissues that were contoured included both lungs (as the total lung volume), heart, spinal cord and esophagus. The CTV included the entire GTV plus 0.7 cm and the PTV included CTV plus another 0.7 cm added margin. PTV44 was treated with parallel-opposed anterior-posterior fields and PTV60 was treated with any combination of fields depending on the spinal cord constrain. If RT had to be delayed for more than 7 days, the patient was withdrawn from the study. Patients with evidence of progression at any time were removed from the study, but continued to be evaluated for survival and toxicity. Survival and time to recurrence or progression were measured from the date of the first treatment session.

Response assessment and follow-up

Complete and partial responses were based on RECIST criteria and toxicity was graded according to RTOG/EORTC criteria. Follow-up visits were every 2 months during the first year and then every 3 months. In the sequential arm, responses were assessed 8 weeks after the end of RT. In the concurrent arm, responses were assessed 8 weeks after the end of the consolidation chemotherapy. Imaging studies (x-ray and/or CT) could be repeated at all times when clinically indicated.

Statistics

Differences in patient demographics between the two arms were assessed with x^2 test and Student's t-test. Further differences in DFS and OS were assessed with Kaplan-Meier survival curves and the significance between the different analyzed parameters, prognostic factors and the survival were analyzed by log-rank and Wilcoxon test and log-rank-Cox/Mantel test. All statistical analyses were performed in Stat Direct, version 11.2.1. A p value <0.05 was considered significant.

Results

One hundred and ten patients were identified from our database. Of these, 25 were excluded from analysis: 7 had metastatic disease, 7 had

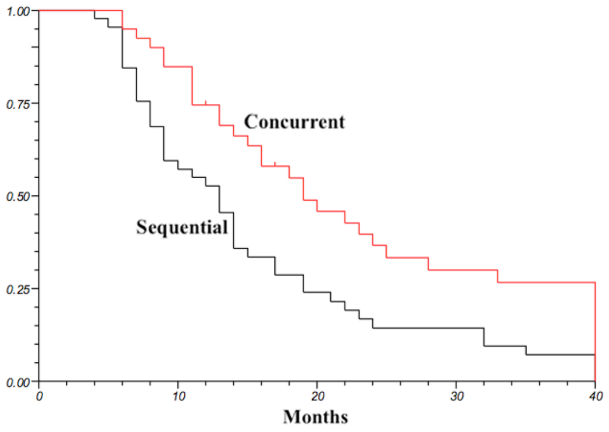

Figure 1. Overall survival according the treatment arm (p=0.0039).

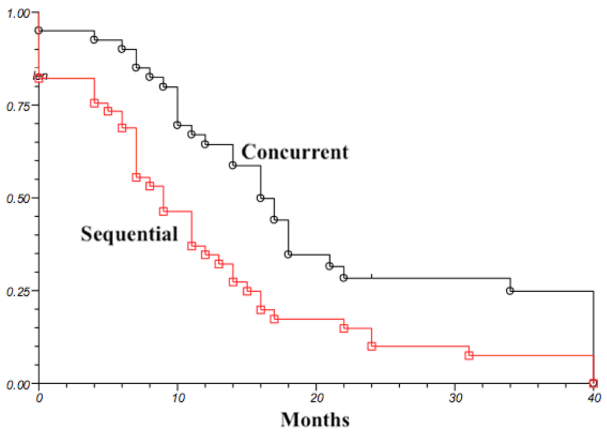

Figure 2. Disease-free survival according the treatment arm (p=0.0023).

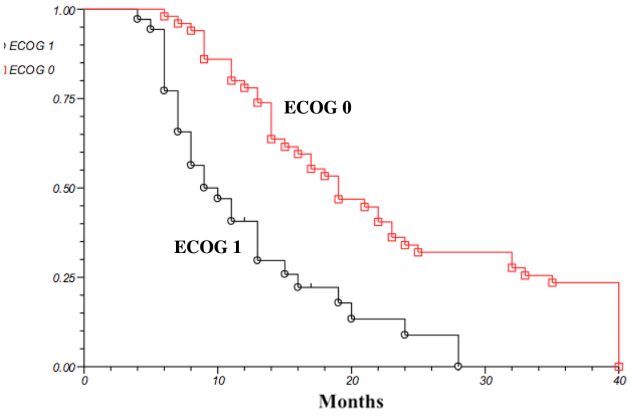

Figure 3. Survival according to ECOG performance status (p<0.001).

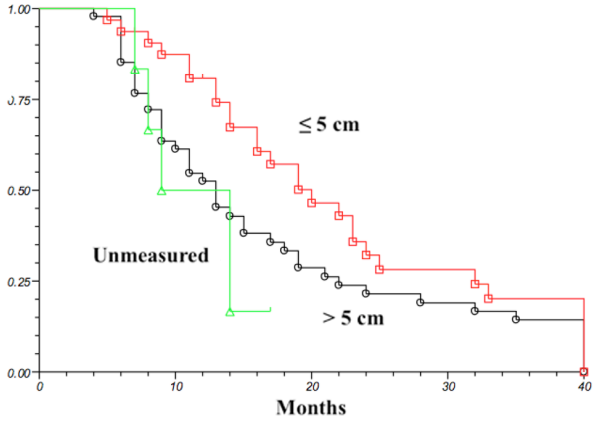

Figure 4. Survival according to tumor size (p<0.029).

sudden deterioration of their general condition, 3 patients had pleural effusion, loss of data or loss of any contact -3 patients, and 5 patients due to delivered tumor dose less than 60 Gy. Eighty-five patients were subsequently included for further analyses. The characteristics of 85 patients are listed in Table 1.

Survival was analyzed until March 2010. The median OS was 13 months in the sequential arm (95% CI 10.2-15.7), and 19 months in the concurrent treatment arm (95% CI 13.6-24.3), with statistically significant difference (log-rank test, p=0.0039; Figure 1). The 1, 2 and 3-year OS rates were 74, 36 and 27% in the concurrent arm and 52, 14 and 7.1% in the sequential arm (p=0.003). DFS for the concurrent arm was 16 months (95% CI 12.7-19.2), and for the sequential arm it was 9 months (95% CI 5.8-12.16). The difference was statistically significant (log-rank test, p=0.0023; Figure 2).

One of the aims of this study was to evaluate the prognostic factors of survival. No analysis was performed according to the treatment modality (sequential or concurrent) because the two groups were homogeneous without significant differences between them.

Most patients were between 44-55 and 56-70 years of age. The youngest patient was 38 years old and the oldest 70 years. The mean age was 58.2±6.68 years. Patients aged between 44 and 55 had median survival of 14 months (95% CI 10.15-17.84), significantly better than the patients between 56 and 70 years of age, with median survival of 10 months (95% CI 4.3-15.6; p<0.05).

As expected, ECOG PS had important impact on survival. OS for patients with ECOG 0 was 19

Table 1. Patient and disease characteristics

Characteristics	*Concurrent chemoradiotherapy arm (N=40) N (%)*	*Sequential chemoradiotherapy arm (N=45) N (%)*	*p value*
Age, years			0.13
18-43	0	1 (2)	
44-55	20 (50)	13 (29)	
56-70	20 (50)	32 (71)	
Sex			0.98
Male	35 (88)	40 (89)	
Female	5 (12)	5 (11)	
Performance status			0.19
0	26 (65)	23 (51)	
1	14 (35)	22 (49)	
Weight loss (%)			0.13
<5	26 (65)	23 (51)	
5-10	14 (35)	22 (49)	
Histology			0.26
Squamous cell	22 (55)	34 (75)	
Adenocarcinoma	10 (25)	6 (13)	
Large cell	3 (7)	2 (4)	
Unspecified	5 (1)	3 (6)	
N status			0.93
N1	12 (30)	15 (33)	
N2	25 (63)	27 (60)	
N3	3 (7)	3 (7)	
T status (cm)			0.38
Tumor ≤ 5	13 (32)	18 (47)	
Tumor > 5	27 (68)	20 (53)	
Hemoglobin (g/dl)			0.15
<12	11 (27)	19 (42)	
≥12	29 (73)	26 (58)	
Duration of symptoms (months)			0.29
< 3	2 (5)	0	
3-6	21 (53)	23 (51)	
> 6	17 (43)	22 (49)	

Table 2. Survival according to hemoglobin level

Hemoglobin level (g/dl)	*Median survival (months)*	*12 months (%)*	*24 months (%)*	*36 months (%)*	*Total N (%)*
<12	9	44	14	0	30 (35)
≥12	17	72	29	16	55 (65)
		p = 0.06			85 (100)

Table 3. Treatment toxicity according RTOG/EORTG criteria in the sequential arm and the concurrent arm

Treatment toxicity		*Sequential arm*				*Concurrent arm*			
		Grade 0 N (%)	*Grade 1 N (%)*	*Grade 2 N (%)*	*Grade 3 N (%)*	*Grade 0 N (%)*	*Grade 1 N (%)*	*Grade 2 N (%)*	*Grade 3 N (%)*
Early	Lung	9 (20)	24 (53)	10 (22)	2 (4)	3 (8)	24 (60)	8 (20)	5 (13)
	Esophagus	17 (38)	20 (44)	8 (18)	0	2 (5)	10 (25)	18 (45)	10 (25)
	Hemoglobin	24 (53)	14 (31)	7 (15)	0	35 (88)	4 (10)	1 (2)	0
	Leucocytes	41 (91)	2 (4.4)	2 (4.4)	0	13 (32)	4 (10)	14 (35)	9 (23)
Late	Lung	7 (16)	29 (64)	9 (20)	0	8 (20)	16 (40)	11 (28)	5 (12)
	Esophagus	36 (80)	5 (11)	4 (8)	0	10 (75)	3 (7)	17 (43)	10 (25)

months, significantly better than 10 months for patients with ECOG 1 status (p<0.001; Figure 3).

Another prognostic factor influencing survival was weight loss in the period of 3 months before study inclusion. Median survival in the patient group with weight loss <5% was 16 months (95% CI 12.2-19.7) and was significantly better than 7 months (95% CI 5.5-11.3) in patients with weight loss between 5 and 10% (p<0.001).

Tumor dimension was also an important prognostic factor with statistical impact on survival (p<0.001). Patients with tumor dimension <5 cm had median survival of 20 months (95% CI 13.6-26.3), compared with the survival of 13 months in patients with tumor dimension >5 cm (95% CI 9.8-16.1) and 9 months (95% CI 6.1-13.8) in unmeasured tumors (p<0.029; Figure 4).

Lymph node involvement also showed statistical influence on the survival of lung cancer patients treated with chemoradiotherapy. Patients with N1 disease lived longer (median 20 months, 95% CI 11.1-32.8), compared to 13 months (95% CI 9.6-16.3) in patients with N2 disease and 7 months (95% CI 5.8-8.1) in patients with N3 disease (p<0.001).

Another parameter we analyzed in this study was hemoglobin level. Patients with hemoglobin level <12g/dl had mean survival of 9 months (95% CI 6.5-11.4), while those with hemoglobin level >12g/dl had mean survival of 17 months (95% CI 12.9-21.1). One-, 2- and 3-year survival rates for each hemoglobin level (<12g/dl vs >12g/dl) were highly different but still without statistical significance (p=0.06, Table 2).

Histological type of lung tumors, gender and duration of symptoms before starting treatment had no significant influence on survival.

Toxicity

The incidence of acute grade 2 and 3 radiation pneumonitis and radiation esophagitis was more frequent in the concurrent chemoradiotherapy arm. Radiation-induced esophagitis was the reason that 5 patients interrupted RT within the allowed period of one week, without excluding them from study. Anemia was most frequent in the sequential arm, while febrile neutropenia developed in 9 patients in the concurrent arm, usually in the period of administration of two cycles of consolidation chemotherapy. Treatment-related toxicities are presented in Table 3.

Discussion

Our study compared sequential and concurrent chemoradiation therapy in locally advanced NSCLC. We found more benefit with concurrent therapy in comparison to previous trials [6,7] with statistical significance in terms of OS and DFS (19 vs 13; 16 vs 9 months, respectively). When our study was designed, the cisplatin-etoposide combination was mostly used concurrently with RT. Consolidation chemotherapy with two cycles of carboplatin-etoposide was administered in the concurrent arm to balance the dose of platinum-based chemotherapy in the two arms. This consolidation chemotherapy administered after concurrent chemoradiotherapy seems promising in terms of survival, as shown in the Southwest Oncology Group (SWOG) S9504 [8] and Locally Advanced Multimodality Protocol (LAMP) [9] studies. Although many reports have analyzed prognostic factors in metastatic NSCLC, fewer have focused on stage III disease [10]. In 1995 Jeremic and Shibamoto [11] evaluated prognostic factors among 169 stage III NSCLC patients treated with hyperfractionated thoracic RT 64-68 Gy with or without etoposide and/or carboplatin chemotherapy. In their multivariate analysis, Karnofsky PS ≥80%, weight loss ≤5%, lower disease stage, younger age (<60 years) and female gender were associated with improved survival. Wigren [12] used a database of 210 patients to develop an index of prognostic factors to stratify the patient population into six different groups with significantly differing median survival times.

Age was not predictive for survival in the present study and our data are consistent with several recent trials suggesting that elderly patients showed response rates and survival outcomes similar to their younger counterparts [13,14] and reporting that elderly patients with inoperable NSCLC manifested local disease recurrence, while younger patient showed distant dissemination, like in our study. According to a number of authors [15,16], gender did not influence survival, but in other trials long-term survival was significantly better in females [17,18]. The latter was not confirmed in the present study.

According to our study, histological type of NSCLC did not influence survival, which is in accordance with the literature. Patients with adenocarcinoma had 45 months median survival time for all stages of disease, and patients with squamous histology had median survival of 44 months, without statistical differences [12,19,20].

This study showed that tumor size was an important factor influencing survival. Patz et al. have previously reported that there was only correlation between tumor size and local disease control,

without influence on survival [21].

According to the literature, the most important prognostic factor for survival was the PS, first reported by Zelen in 1973 [22]. The RTOG [17] analyzed 1592 patients with locally advanced NSCLC treated between 1983 and 1987 with thoracic RT alone. The single most important factor for survival was Karnofsky PS with the cut-off point being 70%. This report, like the report of Wigren [12] has limited value today, as the current standard of care in patients with good PS is combined chemoradiation. Another trial that combined chemotherapy with RT confirmed that PS is an important prognostic factor [18]. We also confirmed that the baseline PS had statistically significant influence on survival.

In our study, OS in the patient group with weight loss <5% was 16 months, significantly better than the 7 months in the patient group with weight loss between 5 and 10%. This result coincides with data from the literature [23,24].

The observation regarding the impact of baseline hemoglobin is of interest. Anemia has been identified as a significant predictor of survival in advanced, metastatic NSCLC [25]. Socinski et al. in a combined modality trial of the Cancer and Leukemia Group B (CALGB) clearly suggest improved survival in patients with hemoglobin values >12g/dl [26]. In the present study we did not confirm this but there was a strong trend for statistical significance between the two groups (p=0.06). Unfortunately, this analysis did not evaluate changes in hemoglobin during therapy and what impact this might have on survival. According to our study, effort should be exercised to maintain hemoglobin level as high as possible, taking into consideration that optimal cell oxygenation is an important factor for local tumor control, and indirectly for survival.

Conclusion

We highly recommend precise definition of the stage of disease and the prognostic factors in NSCLC patients in the hope that a precisely selected patient group might attain better treatment outcomes.

Given the high toxicity in the concurrent-consolidation schedule, this should be reserved for patients younger than 70 years, having good PS and minimal weight loss. In this study, the dose-limiting toxicity (esophagitis) was reduced by performing conformal radiotherapy.

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