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Radiotherapy Versus Radiotherapy Enhanced By Cisplatin In Inoperable Nonmetastatic Nonsmall Cell Lung Cancer (NSCLC): Preliminary Results Of A Randomized Study

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✔ Csplatin (cis–diamminedichloroplatinum) has been reported to enhance the cell killing effect of radiation, an effect whose intensity varies with the schedule of administration. We randomly assigned 53 patients with nonmetastatic inoperable nonsmall cell lung cancer to one of two treatments; radiotherapy for 6–7 weeks (2 Gy given 32 times, in five fractions a week) or radiotherapy in the same schedule, combined with 20 mg/m^2 cisplatin, given on days 1–5 of the second and sixth treatment weeks. An overall response rate of 48% was observed in radiotherapy alone group and 64% in the combined treatment groups. Median time to progression was 8 months for radiotherapy alone group and 10 months for the other group. One–year survival rates were 45% and 60%, respectively. Toxicity was acceptable and no treatment related death occured in either treatment schedule. In this study no significant advantage of the combined treatment over radiotherapy alone was found.

Key words: Non–small cell lung cancer, cisplatin, radiotherapy, radiosensitizer.

✔ Bu çalışmada sisplatinin (cis–diamminedichloroplatinum) radyoduyarlığı artırıcı etkisi değerlendirilmiştir. Bu amaçla hastalar iki randomize gruba ayrılmış; birinci gruba standart fraksiyone radyoterapi (günde 2 Gy'den 6–7 haftada 64 Gy), ikinci gruba ise radyoterapiye ek olarak tedavinin 2. ve 6. haftaları tedaviden bir saat önce 5 gün süre ile 20 mg/m^2 sisplatin verilmiştir. Tek başına radyoterapi grubunda %48 yanıt elde edilirken, bu oran kombine tedavi grubunda %64'tür (p>0.05). İki grup arasında yineleme yerleri bakımından bir farklılık saptanamamıştır. Medyan progresyon süresi tek başına radyoterapi grubunda 8 ay, kombine tedavi grubunda ise 10 aydır. Bir yıllık yaşam oranı tek başına radyoterapi uygulanan grupta %45 iken, bu oran kombine tedavi grubunda %60 olarak bulunmuştur (p>0.05). Kombine tedavi grubunda tedaviye tolerans oldukça iyi olup; tedaviye bağlı ölüm olayına rastlanmamıştır. Kombine tedavi grubunda elde edilen yanıt ve yaşam oranlarının daha yüksek bulunmasına karşın iki grup arasında istatistiksel olarak anlamlı bir farklılık gözlenmemiştir.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, sisplatin, radyoterapi, radyoduyarlaştırıcı.

The prognosis of inoperable non–small cell lung cancer (NSCLC) is poor and has not changed substantially during the past 30 years. In the favorable group of patients with early disease (Stage T_1–T_2,N_0–N_1) considered inoperable for medical reasons, radiotherapy achieves a 5–year survival rate of about 20%.[1-3] The 5–year survival rate in cases of locally advanced disease (stage T_3–T_4 N_2–N_3) is between 5 and 10%[4]. These disappointing results can be partially explained by local recurrences[4]. It is difficult to establish a reliable dose–response curve, however, because of problems encountered

in assessing tumor regression and local tumor control. The upper dose limit is set by the occurance of tissue damage which also depends on the choice of radiation fields. Because local disease recurs in at least 40 to 60 percent of patients given high-dose radiotherapy, there is a need for methods of enhancing or potentiating radiation damage in tumors, such as the use of radiosensitizers[5].

In early 1980s, cisplatin (cis-diammine-dichloro-platinum) was heralded as a drug that could possibly increase radiation-induced damage to tumors. Possible mechanisms of included radiosensitization of hypoxic cells, inhibition of repair of sublethal or potantially lethal damage, increased induction of chromosomal aberrations, and binding to thiols[6]. In vitro results were confirmed by studies in animals[7,8]. The optimal dose and schedule for combination treatment with radiation and cisplatin has not been precisely established[6]. Administering cisplatin shortly before or shortly after daily irradiation is considered to have the greatest tumoricidal effects[5].

In the literature, some favorable results are reported in randomized studies invoving radiotherapy and cisplatin in inoperable tumors using different dosages and schedules[9,10,11]. In light of these data, a randomized trial was started to compare fractioned radiotherapy alone (64 Gy/32 fractions/6.5 weeks) versus same radiotherapy plus cisplatin (20 mg/m^2 iv. days 1-5 of the second and sixth treatment weeks before radiotherapy) at our institute.

MATERIAL AND METHODS

1. Selection criteria

Patients were included in the trial if they had inoperable NSCLC in Stage I, II or III that had been confirmed histologically; had no evidence of distant metastases on clinical or biochemical examination; were no more than 70 years old; had medical contraindications to operation (stage I and II); had a performance status of 2 or less according to the scales of the Eastern Cooperative Oncology Group; and a creatinine <1.5 mg/100 ml.

All patients were staged by physical examinaton, hematological and biochemical liver tests, broncoscopy, chest x-ray standart films and CT-scan of the thorax. Liver ultrasound, bone scan and CT-scan of the brain were performed if suspected distant metastases.

2. Treatment

After informed consent was obtained from eligible patients, they were randomly assigned to one of two treatment groups. The first group received radiotherapy alone. Radiation was delivered with high energy photon beams from a Cobalt-60 unit(*). The total dose delivered was 64 by 32 daily fractions, 5 franctions perweek. The terget volume included the primary tumor, with 2 cm margins, ipsilateral hilum and mediastinum from the sternal notch to 5 cm below the carina. Inferior mediastinal nodes were included in cases with lower lobe tumors and the supraclavicular nodes were included when the upper lobe bronchus was involved by the primary tumor or when the supraclavicular nodes were involved. Patients were treated using anteroposterior fields during the 25 fractions and subsequently with two to three computer posterior fields during the 25 fractions and subsequently with two to computer planned fields. Supraclavicular nodes were treated with an anterior part. The maximum permissible dose to the spinal cord was 50 Gy.

The second treatment group received the same radiotherapy as the first group; ra-

(*) Theratronics 780 C

diotherapy was combined with cisplatin in a dose of 20 mg per square of bodysurface area, given intravenously on days 1-5 of second and sixth treatment week, after parenteral prehydration with one liter of 2.5 percent glucose in 0.45 percent sodium chloride

During treatment, blood tests were performed and creatinine was measured once a week in patients in the combined treatment group.

3. Evaluation of response and toxicity

Patients' responses and acute and late toxic reactions were evaluated according to the criteria of the World Health Organisation[12]. After treatment, the patients were observed at two-month intervals during the first year and at three-month intervals thereafter. Chest x-rays and CT-scans were observed for the assessment of response. Histologic confirmation were not mandatory for the definition of complete response.

4. Statistical analysis

The study was designed as a prospective, randomized two-group trial. Survival curves were calculated according to the Kaplan-Meier technique. Comparisons were made by the log-rank test; this allowed the curves to be compared as a whole[13].

RESULTS

Between January 1993 and November 1994, 53 patients with NSCLC were entered in the study. Three patients who were lost to follow-up a short time after completion of therapy (one in the radiotherapy alone group and two in the combined treatment group) were not evaluable for response. Fifty patients (25 in each group) were evaluable for response and toxicity, 53 for survival.

Patient characteristics are shown in Table I. Fifty-one were males and two were females with a median age of 59.5 years and a median performance status of 1. Forty-one patients had squamous cell carcinoma, 8 adenocarcinoma and 4 large cell carcinoma. The two groups of patients were homogeneous for age, sex, performance status and weight loss during the previous 6 months. All the 50 evaluable patients completed the planned treatment. Analysis was performed after a minimal follow-up period of 12 months.

1. Response

An overall response rate of 48%, was observed in the radiotherapy alone group and 64% in the combined treatment group; a difference which is not statistically significant. Patterns of response are shown in Table II.

2. Survival

Survival was improved by adding cisplatin to radiotherapy. In the radiotherapy along group, the mean survival rate was 45% at one year; in the combined treatment gro-up, 60%. However, difference between two groups was not statistically significant (Fig. 1).

3. Sites of relapse

Patients were classified according to the type of first recurrence, whether local, distant or both (Table III). No significant difference in the pattern of relapse was noted in the two treatment groups. The sites of distant metastases were recorded to be as follows, respectively for the radiotherapy and radiotherapy-cisplatin arm: brain 3/1, bone 2/2, and liver 1/1. The time to local and distant progression was longer in the group given cisplatin. The difference however, was not statistically significant (Fig. 2).

Table–I : Patient characteristics

	Radiotherapy	Radiotherapy+ Cisplatin
Total number of patients	26	27
Male/Female ratio	25/1	26/1
Median age (range)	60 (47-70)	59 (41-70)
Median performance status (ECOG)	1	1
Histology		
Squamous cell	20	21
Adenocarcinoma	4	4
Large cell	2	2
Tumor stage[17]		
T_1	–	1
T_2	3	3
T_3	15	16
T_4	8	7
N_0	7	6
N_1	1	2
N_2	18	18
Weight loss>10%	2	2
Patients not evaluable	1	2
Patients evaluable	25	25
Recruitment distribution per year		
1993	11	12
1994	15	15

Table–II: Response to treatment

Response	Radiotherapy	Radiotherapy +Cisplatin
Complete remission	1	4
Partial remission	11	12
No change	11	8
Progression	2	2

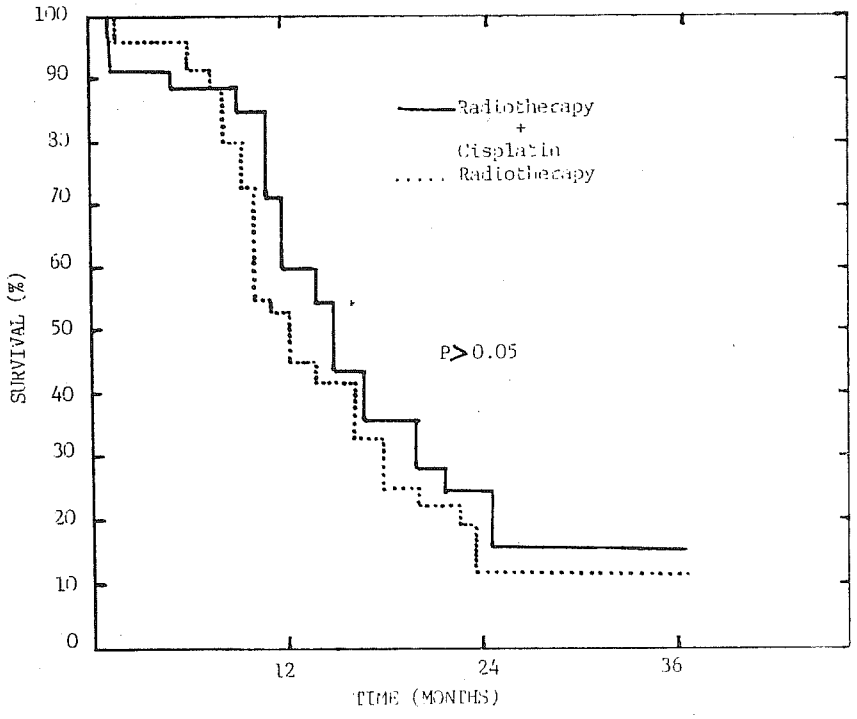

Fig-1 : Overall survival time

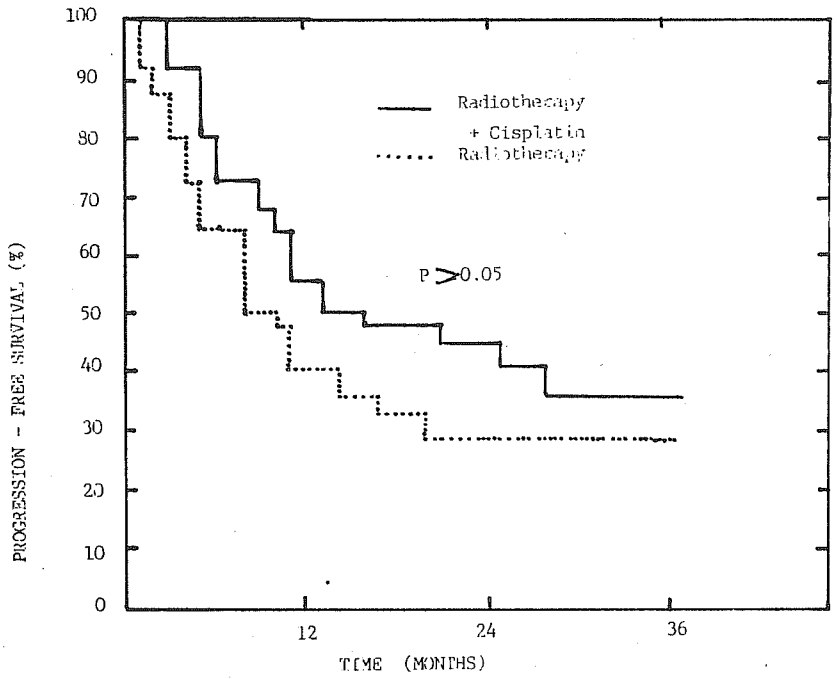

Fig-2 : Progression-free survival time

Table-III: Sites of relapse

First Relapse	Radiotherapy	Radiotherapy+ Cisplatin
Local	9	8
Local + distant	2	2
Distant	6	4

Table-IV: Toxicity

Reaction	Radiotherapy	Radiotherapy+ Cisplatin
Early reaction		
Esophagitis	1	2
Nause and vomiting	5	16 (1)
Renal toxicity	–	–
Hemoglobin	2	3
Leukopenia	3	5 (1)
Late reaction		
Radiotherapy injury	11	12

( ); Grade III toxicity

4. Toxicity

The incidence of esophagitis resulting from the combined treatment was not increased. The main toxic reactions during treatment were nausea and vomiting among the patients who received cisplatin. Hematologic complications were few and seldom worse than grade II reactions (Table IV). The rate of late toxic reactions (more than 6 months after treatment) was not increased by the addition of cisplatin. The rates of pneumonitis,fibrosis and respiratory symptoms were similar in the two treatment groups.

DISCUSSION

The local control rate of inoperable non-small cell lung cancer treated with high dose, conventionally administered, radiotherapy is still relatively low. Depending on prognostic factors and radiation dose it varies between 35 and 42%[1,4,9,12]. Several trials in which chemotherapy was combined with standart radiotherapy have been conducted but no clear evidence in favor of this approach has emerged[14-16]. An agent that deserves special attention as a radioenhancing drug is cisplatin, but its real effectiveness on local control and the best ti-

ming of the combined treatment have yet to be assessed.

Recently, three randomized trials involving radiotherapy and cisplatin in locally advanced non-small cell lung carcinomas using different dosages and schedules have been published[9-11]. In the randomized study by Soresi et al, cisplatin was given weekly during the radiotherapy course[10]. They reported that although no statistically significant differences in median survival time and progression-free interval were seen when radiotherapy alone and radiotherapy combined with weekly cisplatin, a smaller number of intrathoracic relapses was observed in the combined treatment group.

In the study reported by Schaake-Koning and associates from the European Organisation for Research and Treatment of Cancer, either daily low doses or weekly doses of cisplatin plus radiotherapy were used[9]. They found little difference in the median survivals of three groups (radiotherapy alone, radiotherapy-daily cisplatin and radiotherapy-weekly cisplatin) but three-year survivals were significantly improved by giving concomitant daily or weekly cisplatin compared to radiotherapy alone group. The other two groups received same radiotherapy combined with concomitant cisplatin, 30 mg/m^2 given on the first day of each treatment weekly; or 6 mg/m^2 of cisplatin given daily before radiotherapy. This study also showed highly significant improvement in local-regional control in the rediotherapy and cisplatin groups as compared with the radiotherapy alone. The improved local control with cisplatin was associated with better survivals. However, their daily cisplatin group had a 16% three year survival which was compared to 2% in the radiotherapy alone group which received a split course of radiotherapy (3 Gy x 10 fractions/3-4 week break followed by 2.5 Gy x 10 fractions) which may have resulted in a lower survival rate than similar or higher total doses with a split.

In another study, cisplatin was given daily during the short course radiotherapy [11]. 173 patients were randomized to receive radiotherapy 45 Gy in 15 fractions over 3 weeks (Arm A) or same radiotherapy with concomitant low-dose continuous cisplatin (6 mg/m^2) (Arm B). There was no significant difference between the arms in response, progression-free interval, survival, or patterns of failure.

In our study, patients were treated with high dose, conventional radiotherapy. Cisplatin dose was increased to 20 mg/m^2. Although the number of patients is too small to allow conclusions to be drawn, complete responses were observed more frequently in the group of patients treated with radiotherapy and cisplatin. Furthermore, local and distant progressions were observed at a later time in patients treated with cisplatin than in patients treated with radiotherapy alone. In this randomized study, preliminary results of combined treatment group confirm those obtained in the other studies as regards both response rate and survival, but without showing any statistically significant differences for the two treatment modalities in terms of response rate, survival and sites of relaps.

The question of the clinical effectiveness of using cisplatin as a radioenhancer remains unanswered. The conflicting results of the clinical trials suggest that the optimum scheduling of the two modalities has not yet been achieved. The encouraging results of some of the trials and the intractability of the disease suggest that further efforts should be made to optimize clinical

trial protocols, perhaps by reviewing the radiobiological and pharmacological bases of the combined treatment or by adding other chemotherapeutic agents[11].

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