Concurrent Radiochemotherapy with Vinorelbine plus Cisplatin or Carboplatin in Patients with Locally Advanced Non-Small-Cell Lung Cancer (NSCLC) and an Increased Risk of Treatment Complications

Preliminary Results

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Background: In elderly patients, patients with multiple morbidities, and patients with a reduced general condition, the standard treatment of inoperable non-small-cell lung cancer (NSCLC) consists of either chemotherapy or radiation therapy alone and is associated with an extremely poor prognosis. We therefore investigated the feasibility, toxicity, and efficacy of radiotherapy with concurrent chemotherapy using vinorelbine plus cisplatin or carboplatin in NSCLC patients at risk for treatment complications.
Patients and Methods: A total of 33 patients (six women, 27 men, median age 65 years) with locally advanced, functionally inoperable pulmonary carcinomas, recurrent lung cancer or postoperative macroscopic residual tumors (R2) with an increased risk of treatment complications (WHO performance status 2/3; cardiac, renal or pulmonary failure; marked pretherapeutic weight loss; age between 71–75 years) received 12.5 mg of vinorelbine per m^2 body surface area (BSA) on days 1, 8, 15, 29, 36 and 43 plus either cisplatin 20 mg/m^2 BSA (ten patients) or carboplatin 70 mg/m^2 BSA (23 patients) on days 1–5 and 29–33 together with conventionally fractionated radiotherapy. The tumor regions were irradiated with doses of up to 63 Gy (90% isodose), and potentially affected lymph nodes received doses of up to 45.0 or 50.4 Gy (90% isodose).
Results: Briefly, 31 of 33 patients successfully completed radiation therapy and 26 received four cycles of vinorelbine plus at least two cycles of cisplatin or carboplatin. Hematotoxic side effects included grade III leukocytopenia (n = 8), grade III thrombocytopenia (n = 5), and grade IV thrombocytopenia (n = 2). Other side effects consisted of peripheral neuropathy grade III (n = 1) and esophagitis grade IV (n = 1). Severe pneumonitis did not occur. Six patients had pneumonia before radiochemotherapy. 21 patients (63%) exhibited a complete (n = 7) or partial response (n = 14) to chemoradiation. The twelve nonresponders had either stable (n = 9) or progressive disease (n = 3). The survival rates plus standard deviations were as follows: 1-year survival: 60 ± 8%, 2-year survival: 36 ± 9%, 3-year survival: 24 ± 9%, median survival time: 17 months (5;29 months; 95% confidence interval [CI]), median progression-free survival: 11 months (9;13 months; 95% CI). The median follow-up time was 14 months.
Conclusion: Conventionally fractionated radiochemotherapy with vinorelbine plus a platinum derivative is feasible in patients with NSCLC and increased risk of treatment complications. Compared to patient populations described in the literature, the survival rates achieved by concurrent radiochemotherapy appear to be better than those achieved with radiotherapy alone.

Key Words: Non-small-cell lung cancer · Concurrent radiochemotherapy · Cisplatin · Carboplatin · Vinorelbine

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Simultane Radiochemotherapie mit Vinorelbin und Cisplatin/Carboplatin bei Patienten mit lokal fortgeschrittenem NSCLC und erhöhtem Behandlungsrisiko. Erste Ergebnisse

Hintergrund: Eine alleinige Bestrahlung oder Chemotherapie ist therapeutischer Standard bei multimorbiden, alten oder im Allgemeinzustand reduzierten Patienten mit inoperablen nichtkleinzelligen Bronchialkarzinomen (NSCLC). Die Prognose ist außerordentlich schlecht. Deshalb untersuchten wir die Durchführbarkeit, Toxizität und Wirksamkeit einer simultanen Radiochemotherapie mit Vinorelbin und Cisplatin oder Carboplatin bei Patienten mit NSCLC und erhöhtem Behandlungsrisiko.
Patienten und Methodik: 33 Patienten (sechs Frauen, 27 Männer, medianes Alter 65 Jahre) mit einem lokal fortgeschrittenen, funktionell inoperablen Bronchialkarzinom, Bronchialkarzinomrezidiv oder postoperativem makroskopischen Residualtumor (R2) mit erhöhten Behandlungsrisiken (WHO-Performance-Status 2/3 oder kardiale oder renale oder pulmonale Insuffizienz oder aus-

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geprägter prätherapeutischer Gewichtsverlust oder Alter zwischen 71 und 75 Jahren) erhielten 12,5 mg/m^2 Körperoberfläche (KO) Vinorelbin an den Tagen 1, 8, 15, 29, 36 und 43 sowie Cisplatin 20 mg/m^2 KO (zehn Patienten) oder Carboplatin 70 mg/m^2 KO (23 Patienten) an den Tagen 1–5 und 29–33 zusammen mit einer konventionell fraktionierten Strahlentherapie der Tumorregionen bis 63 Gy (90%-Isodose) und potentiell befallener Lymphknoten bis 45,0 bzw. 50,4 Gy (90%-Isodose).

Ergebnisse: Die Bestrahlung wurde bei 31 von 33 Patienten in voller Dosierung und die Chemotherapie bei 26 Patienten mit mindestens zwei Kursen Cisplatin oder Carboplatin und vier Kursen Vinorelbin durchgeführt. Hämatotoxische Nebenwirkungen schlossen Leukozytopenien Grad III (n = 8), Grad-III-Thrombozytopenien (n = 5) und Grad-IV-Thrombozytopenien (n = 2) ein. Sonstige Nebenwirkungen: periphere Neuropathie Grad III (n = 1) und Ösophagitis Grad IV (n = 1). Es war keine höhergradige Pneumonitis zu verzeichnen. Sechs Patienten hatten eine Pneumonie, die jeweils bereits vor Therapiebeginn bestand. 21 Patienten (63%) zeigten entweder eine komplette (n = 7) oder eine partielle Remission (n = 14) auf die Radiochemotherapie. Die zwölf Patienten ohne Therapieansprechen hatten entweder eine „stable disease" (n = 9) oder waren progredient (n = 3). Die Überlebensraten einschließlich Standardabweichungen betrugen: 1-Jahres-Überlebensrate: 60 ± 8%, 2-Jahres-Überlebensrate: 36 ± 9%, 3-Jahres-Überlebensrate: 24 ± 9%, mediane Überlebenszeit: 17 Monate (5;29 Monate; 95%-Konfidenzintervall [KI]), medianes progressionsfreies Überleben: 11 Monate (9;13 Monate; 95%-KI). Die mediane Nachbeobachtungszeit lag bei 14 Monaten.

Schlussfolgerung: Eine konventionell fraktionierte Radiochemotherapie mit Vinorelbin und einem Platinderivat ist bei Patienten mit NSCLC und erhöhten Therapierisiken durchführbar. Verglichen mit aus der Literatur bekannten Ergebnissen einer alleinigen Bestrahlung scheinen durch eine simultane Radiochemotherapie bessere Überlebensraten möglich.

Schlüsselwörter: Nichtkleinzelliges Bronchialkarzinom · Simultane Radiochemotherapie · Cisplatin · Carboplatin · Vinorelbin

Introduction

Compared to sequential radiotherapy-chemotherapy [3, 6–9] or radiation therapy alone [10, 29], concurrent radiochemotherapy was found in most studies to significantly improve the survival of patients with small-cell lung cancer or with functionally or locally inoperable non-small-cell lung cancer (NSCLC). In patients with UICC stage III NSCLC, radiotherapy alone was found to achieve a median survival rate of only 9–12 months compared to 15–18 months with concurrent radiochemotherapy. It has to be considered that only patients < 70 years who are in good general health were included in these protocols. There is no differentiated data available on concurrent radiochemotherapy in patients with unfavorable starting conditions, such as extensive weight loss, concomitant cardiac, renal or pulmonary diseases, or old age. However, it is an undisputed fact that radiotherapy or chemotherapy alone achieves poor results in these patients.

Most patients with surgically untreatable lung cancer have multiple concomitant diseases, reduced general health, limited respiratory or pulmonary function, and a tendency to develop pneumonia. Treatment of these patients generally consists of radiation therapy alone, chemotherapy alone, or supportive-palliative treatment. Concurrent chemotherapy with radiotherapy often is not deemed a viable option, since it is considered to be too toxic for these patients.

Within the past few years, new drugs such as vinorelbine and taxanes have become established in the treatment of NSCLC. Since all of these proven substances exhibit a favorable spectrum of side effects, the potential benefit of combining these drugs with radiation therapy is worth being investigated.

The aim of the present study was to develop a concurrent radiochemotherapy protocol for use in NSCLC patients susceptible to treatment complications. Here, we will report our preliminary feasibility, toxicity and efficacy data for this study.

Patients and Methods

Patient Population and Characteristics

Between June 30, 1997 and January 31, 2002, 33 patients (six women, 27 men) with a functionally inoperable NSCLC, a relapse of the same, or postoperative residual NSCLC (R2) without distant metastases underwent concurrent radiochemotherapy (vinorelbine plus cisplatin or carboplatin) at the Department of Radiotherapy, Rostock University Hospital, Germany. The patients' median age was 65 years (39–75 years). The cutoff date for inclusion in the analysis was August 1, 2002.

To be treated according to the protocol, the patient had to fulfill at least one of the risk criteria listed in Table 1. This protocol was not used in patients of advanced age until mid 1999. The age limit has meanwhile been raised to 78 years. Table 2 shows the characteristics of the patient population, especially the type of cumulative risk factors present in the majority of patients.

Inoperable patients with better starting conditions were irradiated in the same manner, but their concurrent chemotherapy was carried out using CPT11 and cisplatin. These results were published in a separate article.

In each case, the primary tumor or regional lymph node metastases were staged by bronchoscopy, chest X-ray, and

Table 1. Treatment risk factors and inclusion criteria. FEV_1: forced expiratory volume in l/s; NV: normal value; VC: vital capacity in l.

Tabelle 1. Risikofaktoren der Behandlung und Einschlusskriterien. FEV_1: forcierte exspiratorische 1-s-Kapazität in l/s; NV: Normalwert; VC: Vitalkapazität in l.

	Reduced general condition (equivalent to WHO performance score of 2 or 3, latter only applicable if treatment was absolutely indicated)
Or	Distinctive weight loss (≥ 5% of body weight in the 3 months before diagnosis)
Or	Compensated renal insufficiency (creatinine clearance 30–60 ml/min)
Or	Cardiac insufficiency, compensated (no volume load of > 2 l of fluid supply possible)
Or	Pulmonary insufficiency (FEV_1 < 60% of the NV, > 30% of the NV, or VC < 60% of the NV, > 30% of the NV)
Or	Advanced age (71 to 75 years)

Table 2. Characteristics of study population.

Tabelle 2. Patientencharakteristik.

Number	33
Age (years)	
• Median	65
• Range	39–75
WHO performance status	
• 0 and 1	4
• 2	26
• 3	3
Stage	
• I and II	7
• IIIA	4
• IIIB	19
• Relapse	2
• R2 tumor	1
Histology	
• Squamous cell carcinoma	17
• Adenocarcinoma	10
• Other carcinoma and non-small-cell lung carcinoma without further specification	6
Number of risk factors	
• 1	9
• 2	9
• 3	10
• ≥ 4	5

computed tomography (CT) of the thorax prior to chemoradiation therapy. In order to exclude possible distant metastases, all abdominal studies were performed by ultrasound or CT. Most patients had stage IIIA (n = 4) or stage IIIB disease (n = 19), seven had stage I or II disease, two presented with a relapse, and one had macroscopic tumor residue after tumor resection. Prior to radiochemotherapy, all patients with stage I, II and IIIA disease consulted a thoracic surgeon to determine whether primarily surgical treatment or neoadjuvant therapy was needed. The seven patients with stage I or II NSCLC were excluded from surgery due to impaired lung function (n = 4), age (n = 1), impaired performance status (n = 1), or prior lung surgery (n = 1). All participants gave their written informed consent before starting the treatment.

Radiotherapy

Radiotherapy was carried out using a linear accelerator at 9- or 15-MV photons. The target volume included the region of the primary tumor plus a 1- to 2-cm safety margin as well as the ipsilateral hilar lymph nodes and bilateral mediastinal lymph node sites. Ipsilateral supraclavicular lymph nodes were also irradiated in patients with superior pulmonary lobe involvement or extensive mediastinal metastatic disease. In each case, CT imaging was used for three-dimensional radiation treatment planning. Following an isocentric technique, three or four fields were irradiated using customized collimators. After administering 20 Gy, the initial radiation treatment plan was revised as needed based on the CT-determined tumor volume. If tumor shrinkage had occurred, the sizes of the radiation fields were reduced accordingly. The cumulative dose in the lung reached a maximum of 20 Gy. The maximum dose in the area of the spinal cord was 44 Gy. 1.8-Gy fractions (90% isodose, maximum 100%) were administered. Depending on the radiation tolerance of the lung and spinal cord, each patient received a total dose of 45–50.4 Gy – according to the reference point plan of the International Commission on Radiation Units and Measurements (ICRU), this corresponds to a total dose of 47.5–54.0 Gy. Following planning CT, each patient received an additional small-volume boost in the area around the primary tumor. All macroscopic tumors still present at that time were irradiated using an individually selected radiation technique. The booster dose ranged from 12.6 to 18.0 Gy (14–20 Gy according to ICRU 50), depending on the lung and spinal cord tolerance. Thus, the entire macroscopic tumor volume received a dose of 63 Gy (90% isodose; approximately 66 Gy according to ICRU 50); the total dose to the prophylactically irradiated volume was 45–50.4 Gy (90% isodose; approximately 47–53 Gy according to ICRU 50).

Chemotherapy

The prerequisite for chemotherapy was a sufficient bone marrow reserve, defined as leukocytes ≥ 3,000/ml, thrombocytes ≥ 100,000/ml, and hemoglobin (Hb) ≥ 6.0 mmol/l. Preliminary echo- and electrocardiographic studies as well as lung function and creatinine clearance tests were also performed to assess the feasibility of chemotherapy in all patients.

Chemotherapy (Figure 1) consisted of two cycles of cisplatin (20 mg/m^2/day) or carboplatin (70 mg/m^2/day) on days 1–5 and 29–33 plus vinorelbine (12.5 mg/m^2/day) on days 1, 8, 15, 29, 36, and 43. If peripheral cytopenia occurred (leukocytes < 3,000/ml or thrombocytes < 100,000/ml), the scheduled dose fraction of vinorelbine was postponed for 1 day, or for 1 week in the case of cisplatin and carboplatin. Carboplatin was administered as the platinum salt in cases where cardiac com-

pensation limited fluid infusion to < 2 l/day as well as in patients with renal insufficiency (renal clearance < 60 ml/ min, > 30 ml/min) or WHO performance status grade 3. Carboplatin was regularly used instead of cisplatin since the beginning of 2002.

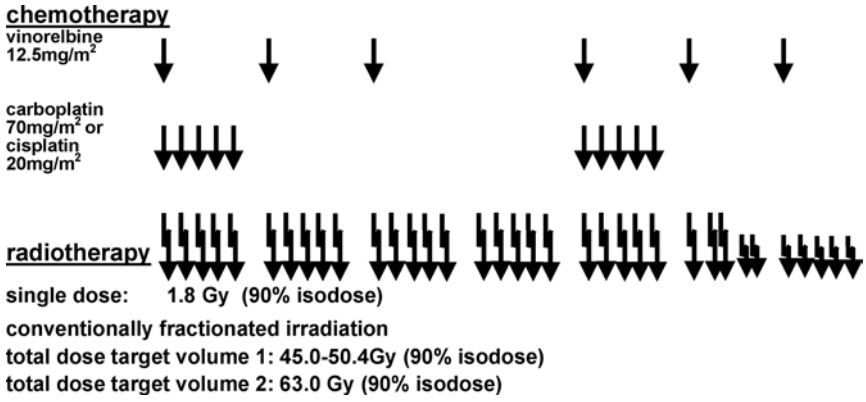

Figure 1. Treatment protocol.

Abbildung 1. Behandlungsschema.

Grading of Side Effects and Efficacy of Treatment

Serious adverse events were graded according to the Common Toxicity Criteria of the Eastern Cooperative Oncology Group (ECOG). The tumor response was documented by comparing X-ray films taken at two different levels before and 6 weeks after completion of radio-chemotherapy (or right at the end of treatment in seven cases) and 3 months after completion of therapy. When feasible, bronchoscopy (eight patients) and thoracic CT imaging (eleven patients) were also performed to assess remission. The outcome was rated as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the WHO definitions.

Statistical Analysis

The clinical data and Kaplan-Meier survival data were calculated using SPSS software. Survival was defined as the time between diagnosis and death or the last follow-up. Progression-free survival was calculated as the time between diagnosis and the detection of new lesions or of tumor residue that persisted until progression occurred.

Results

Remission

Of the 33 patients studied, 21 (63%) exhibited a complete (n = 7) or partial response (n = 14) to radiochemotherapy. Another nine patients (27%) showed no tumor response (stable disease), and three patients developed progressive disease during or shortly after therapy.

Survival

24 of the 33 NSCLC patients studied have died so far. 23 of the deaths were tumor-related, while one death occurred due to hypoglycemia caused by an insulin overdose with suicidal intent. No participant died as a direct result of treatment. The survival figures for the total population, with standard deviations, were as follows: median survival: 17 months (5;29 months, 95% confidence interval [CI]), 1-year survival: 60 ± 8%, 2-year survival: 36 ± 9%, and 3-year survival: 24 ± 9% (Figure 2).

The statistics for the subgroup with stage III NSCLC were as follows: median survival 17 months (4;20 months, 95% CI), 1-year survival 56 ± 10%, and 2-year survival 38 ± 10%. The overall survival of the patients with a relapse, residual tumor or stage I or II NSCLC was notably higher (2-year survival: approximately 56 ± 17%) but not statistically significant (Figure 3).

23 patients were treated with carboplatin/vinorelbine and ten with cisplatin/vinorelbine. The survival curves for the two chemotherapy schedules did not differ significantly. However, the median survival time with carboplatin/vinorelbine was 21 months (7;35 months, 95% CI) compared to only 17 months (2;35 months, 95% CI) with cisplatin/vinorelbine.

Furthermore, we found that patients with three or more classic risk factors (see Patients and Methods and Table 1) tended to have shorter survival times than patients with only one or two risk factors. The latter group survived a median 22 months (0;24 months, 95% CI), whereas those with three risk factors survived a median 17 months (3;31, 95% CI). Patients with four or more risk factors or comorbidities died after a median 11 months (12;32 months, 95% CI). However, only five

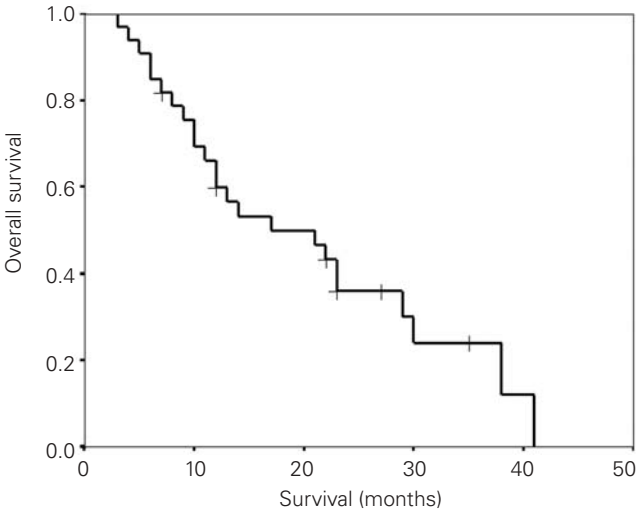

Figure 2. Overall survival.

Abbildung 2. Kumuliertes Gesamtüberleben.

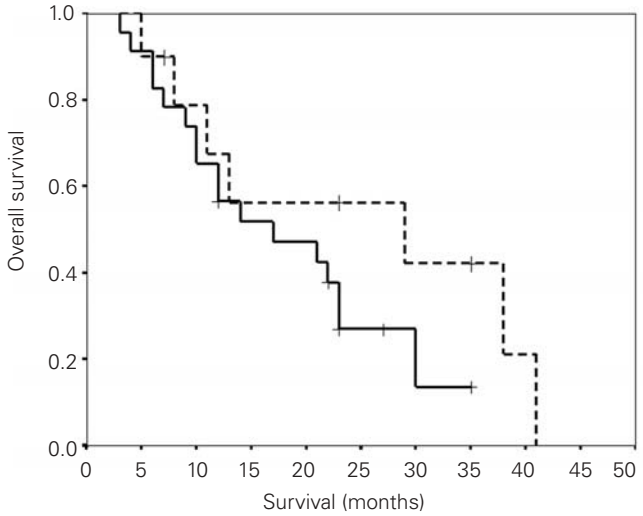

Figure 3. Survival according to UICC criteria (stage III: solid line, stage I/II, recurrences, R2 resection: broken line).

Abbildung 3. Überleben in Abhängigkeit vom UICC-Stadium (Stadium III: durchgezogene Linie; Stadium I/II, Rezidive oder Residualtumor: gestrichelte Linie).

patients with this distinctive risk profile were included in the study (see Figure 4).

The subgroups were also compared to determine whether tumor response had a positive effect on the median survival time. Patients with a complete response survived a median 38 months (18;58 months, 95% CI) and those with a partial response a median 23 months (20;26 months, 95% CI). By comparison, the median survival was only 7 months (4;10 months, 95% CI) in patients with stable disease and 8 months in those with progressive disease (2;14 months, 95% CI; Figure 5).

Analysis of Relapse

Disease progression occurred after a median 11 months (9;13 months, 95% CI). About 42 ± 10% of the patients were still tumor-free at 1-year follow-up, and 19 ± 9% at 2-year follow-up. So far, relapses have been observed in 22 cases, 15 of which were locally restricted tumor recurrences and seven distant metastases. The brain is the organ most susceptible to hematogenous metastatic spread. Three of the seven patients with distant metastases had purely cerebral metastasis, two had cerebral metastasis plus other distant metastases, and two patients had noncerebral distant metastases.

Toxicity

The observed side effects and treatment-related toxicity were manageable. The most severe side effects were hematologic in nature. Grade III leukocytopenia developed in eight patients, but grade IV toxicity did not occur. Five patients developed grade III thrombocytopenia, two patients grade IV thrombocytopenia. Higher-grade anemia did not occur. The median Hb concentration was 8.1 mmol/l (5.7–10.3 mmol/l) at baseline and 7.1 mmol/l (5.0–8.8 mmol/l) at the nadir after the first treatment cycle.

One patient developed a peripheral neuropathy (WHO grade III). Grade III or IV radiogenic pneumonitis was not observed. One patient developed grade IV esophagitis. Six patients received antibiotics for pneumonia during the study; however, each of them had received prior treatment for the same condition before the start of radiochemotherapy.

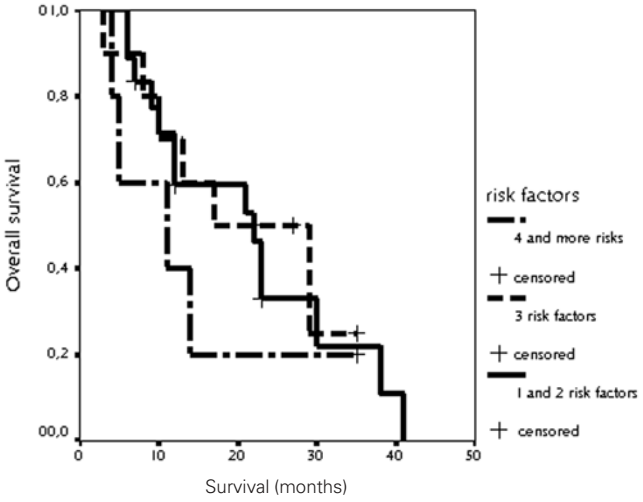

Figure 4. Survival according to the amount of treatment risk factors per patient.

Abbildung 4. Kumuliertes Überleben in Abhängigkeit von der Anzahl der Behandlungsrisiken pro Patient.

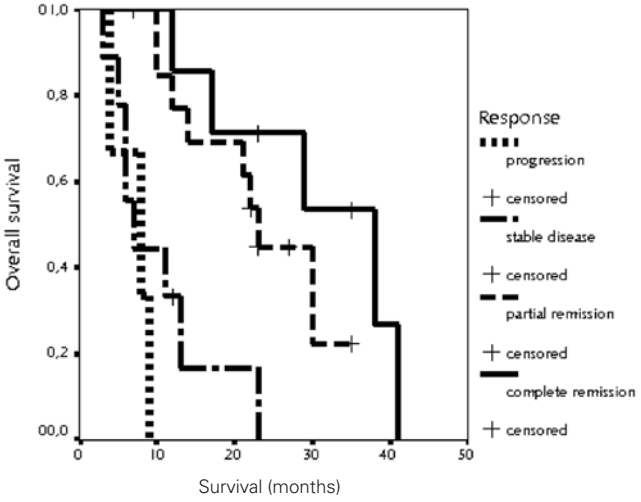

Figure 5. Survival according to remission following radiochemotherapy.

Abbildung 5. Kumuliertes Überleben in Abhängigkeit von der erzielten Remission nach Radiochemotherapie.

Feasibility of Radiochemotherapy

As a whole, 31 of 33 patients (94%) completed radiotherapy according to the protocol. Of those who did not, one patient withdrew from radiotherapy after she had been classified as a candidate for surgical resection provided that she showed stable remission. However, surgery was not carried out in the end. In the second case, radiotherapy had to be interrupted for 2 weeks due to the spontaneous development of pneumothorax of unknown cause. Likewise, most cycles of chemotherapy were administered on schedule, i.e., 43 of 46 (91%) cycles of carboplatin, 20 of 20 (100%) cycles of cisplatin, and 148 of 198 (75%) cycles of vinorelbine.

Discussion

A number of randomized trials have shown that patients with inoperable NSCLC treated with sequential irradiation and chemotherapy and especially with concurrent radiochemotherapy have a significantly better prognosis than those treated with radiation therapy alone [4, 5, 6, 8, 13, 18, 19, 25, 27, 29]. The intensity-modulated radiotherapy offers an opportunity of dose escalation and may provide another tool for improving local control and survival [20].

It is generally assumed that increasing the treatment intensity by administering chemotherapy in addition to radiation therapy does not have a beneficial effect on patients > 70 years of age or patients in a reduced general condition due to concomitant diseases. However, the data on which this assumption is based is limited and partly inconsistent. Our hypothesis that these patients may benefit from concurrent radiochemotherapy is supported by the findings of Lau et al. [17], who reported on 24 stage III NSCLC patients with a poor risk profile (weight loss of > 5% in 3 months, SWOG performance score of 3, and FEV1 < 2 l/s due to moderate to severe pulmonary or renal insufficiency) who could not be treated according to any other protocol. Lau's team found that conventionally fractionated radiation therapy with up to 61 Gy in combination with two cycles of etoposide and carboplatin led to response rates of 87%, a median survival time of 12 months, and an overall 2-year survival rate of 40%. Compared to earlier data, this is significantly better than the survival rates of 9–10 months achieved with radiation therapy alone [22]. By contrast, Jeremic et al. [12], who treated patients > 70 years with concurrent radiochemotherapy, found that the prognosis of patients with a Karnofsky performance status of 70–80 or weight loss of > 5% was much worse than that of old patients without other risks (median survival: 8 vs. 22 months). However, these results are not comparable to ours since all of their patients were > 70 years of age.

By contrast, the meta-analysis of Movsas et al. [21] suggested that intensified treatment protocols resulted in shorter progression-free and median survival of risk patients compared to those treated by radiation therapy alone. However, these findings have to be viewed critically for the following reasons: the statistical analysis of these authors was based on subgroup data from merely two studies [15, 26]. They only found a small number of applicable risk patients in the literature [15, 26]. As far as we can tell, the number of patients barely exceeded 20. Both protocols investigated [15, 26] consisted of lengthy induction chemotherapy with cisplatin plus vinblastine or etoposide followed by concurrent radiochemotherapy using cisplatin. Cumulatively, the overall doses of cytostatics were significantly higher than those used in our study. For example, some patients treated by their protocols had already received as much as 200 mg of cisplatin and 25 mg of vinblastine prior to concurrent radiochemotherapy. This extremely intense protocol has a higher risk of inducing toxicity, especially in patients with a reduced general condition. As a result, the rate of grade III and IV hematologic side effects in the concurrent radiochemotherapy arms of these studies was very high (60%).

Unlike our study, the other analyses do not provide detailed data graded according to cumulative risk factors. One therefore cannot determine the effect of any single risk factor or its cumulative effect on toxicity.

However, daily clinical practice has shown that at least one quarter of all patients with NSCLC also suffer from chronic obstructive pulmonary disease (COPD), 20 of 100 patients have coronary heart disease (CHD) requiring treatment, 22% hypertension, and 13% arteriosclerosis [23]. Due to the numerical significance of this patient population and in light of the poor results achieved by irradiation or chemotherapy alone, it is necessary to develop intensified treatment protocols which are tolerated by and improve the survival of these risk patients.

The following points have to be taken into consideration when developing such treatment variants.

The additional therapy modalities do not necessarily increase the total spectrum of side effects, as is often assumed [21]. For instance, both Komaki et al. [15] and Furuse et al. [8] observed grade III esophagitis in only 6% and 3% of their patients, respectively, and acute pulmonary side effects in only 1%. Likewise, pneumonitis and esophagitis played only a minor role in our patient population.

Radiotherapy has to be planned as optimally as possible. The low rate of local side effects in our patients confirms the benefit of using three-dimensional radiation treatment planning with a multifield technique from the start [30], as well as of adapting the target volume after tumor shrinkage by adjusting the radiation treatment plan after administration of 20 Gy, 45 Gy, and 50.4 Gy.

Induction chemotherapy might lead to higher local toxicity during concurrent radiochemotherapy, as has been described after accelerated hyperfractionated [24, 35] or hypofractionated radiotherapy [32]. Vokes et al. [31] and Zatloukal et al. [34] report that more severe esophagitis occurs in 5–25% of patients after high-dose induction therapy with vinorelbine and a platinum salt.

Especially in patients with a limited performance status, such as in our population, the choice of cytostatics is of ma-

jor importance. Authors performing concurrent radiochemotherapy using newer substances (gemcitabine, paclitaxel, docetaxel, irinotecan, vinorelbine) alone or in combination with a platinum salt have observed significantly varying rates of local side effects. The incidence of pneumonitis reportedly ranges between 75% (gemcitabine 1,000 mg/m^2) [28] and < 5% for paclitaxel/carboplatin [1]. Vinorelbine/platinum salt combinations have a rather favorable spectrum of side effects, as was shown in a phase III study of cisplatin/paclitaxel versus cisplatin/gemcitabine and cisplatin/vinorelbine [31].

In any case, one must ensure that the hematogenic and nonhematogenic side effects of chemotherapy are controllable. Therefore, we used a relatively low single dose of vinorelbine (12.5 mg/m^2), but administered chemotherapy on 6 days during the irradiation period. This allowed us to stop the single applications of vinorelbine if necessary in order to remain below the hematologic limit of toxicity. Since the

Table 3. Results of radiochemotherapy with vinorelbine (VRN) plus cisplatin (CDDP) or carboplatin (CBCDA). ADJ: adjuvant therapy; IND: induction therapy; RCT: radiochemotherapy; RT: radiation therapy; TD: total dose.

Tabelle 3. Ergebnisse der Radiochemotherapie mit Vinorelbin (VRN) und Cisplatin (CDDP) oder Carboplatin (CBCDA). ADJ: adjuvante Therapie; IND: Induktionstherapie; RCT: Radiochemotherapie; RT: Radiotherapie; TD: Gesamtdosis.

Protocol (author)		n	Median survival (MS) Overall 3-year survival (3YS) Response rate (RR)	Incidence of pneumonitis, esophagitis grade 3 and 4
Zatloukal et al. 1998 [33]		20		
IND + ADJ (1 cycle)				
VNR:	25 mg/m^2 on days 1, 8, 15			
CDDP:	80 mg/m^2 on day 1			
RCT (2 cycles)				
VNR:	12.5 mg/m^2 on days 1, 8, 15, q 28		RR: 62.5%	5% of cycles esophagitis; no pneumonitis
CDDP:	80 mg/m^2 on day 1, q 28			
RT:	conventionally fractionated, TD 60 Gy			
Kisohara et al. 2001 [14]		27		None
RCT				
VNR:	20 mg/m^2 on days 1, 8, q 21			
CDDP:	80 mg/m^2 on day 1, q 21			
RT:	modified accelerated with concomitant boost, TD 61 Gy			
Lanfranco et al. 1999 [16]		23		
IND (1 cycle)				
VNR:	30 mg/m^2 on days 1, 8, q 21			
CBCDA:	AUC 6 on day 1, q 21			
RCT (up to 5 cycles)			RR: 53%	10% esophagitis
VNR:	30 mg/m^2 on days 1, 8, q 21		MS: > 13 months	
CBCDA:	AUC 5, on day 1, q 21			
RT:	conventionally fractionated, TD 30–66 Gy			
Vokes et al. 2002 [31], three arms, randomized		181		
IND (2 cycles)				
Arm 1:	gemcitabine: 1,250 mg/m^2 on days 1, 8, q 21 CDDP: 80 mg/m^2 on days 1, 8, q 21			
Arm 2:	paclitaxel: 225 mg/m^2 on day 1, q 21 CDDP: 80 mg/m^2 on days 1, 8, q 21			
Arm 3:	VRN: 30 mg/m^2 on days 1, 8, 15, 22, 29 CDDP: 80 mg/m^2 on days 1, 8, q 21			
RCT (2 cycles)				
Arm 1:	gemcitabine: 600 mg/m^2 on days 1, 8, q 21 CDDP: 80 mg/m^2 on days 1, 8, q 21		MS: 18.3 months 3YS: 28% RR: 74%	52% esophagitis
Arm 2:	paclitaxel: 135 mg/m^2 on day 1, q 21 CDDP: 80 mg/m^2 on days 1, 8, q 21		MS: 14.8 months 3YS: 19% RR: 67%	39% esophagitis
Arm 3:	VRN: 15 mg/m^2 on days 1, 8, q 21 CDDP: 80 mg/m^2 on days 1, 8, q 21		MS: 17.7 months 3YS: 23% RR: 73%	25% esophagitis
RT:	conventionally fractionated, TD 66 Gy			

study was so well controllable, retention pneumonia was not a primary exclusion criterion. If there was no response to antibiotics in the six cases where pneumonia occurred, cytostatic treatment was interrupted until abatement of the pneumonia in order to avoid cytopenic complications. We recommend that other hospitals adapt their treatment methods accordingly.

Because of the low probability of side effects, especially pneumonitis [33], and the expected enhancement of local control, we proposed this chemoradiation schedule to patients formerly classified as ineligible for surgery due to impaired lung function in spite of the lack of published results on concurrent radiochemotherapy in inoperable stage I and II NSCLC.

The patients were assigned to the carboplatin or cisplatin group based on clinical criteria. Cisplatin was initially the first choice in patients with sufficient renal and cardiac function. We did not detect any considerable differences in the frequency of toxicity and intensity of side effects between the two groups. However, the number of cases is still too low for a final assessment. Morbidity was higher in the carboplatin/vinorelbine group, since these patients had three risk factors on average, which were mostly related to renal and cardiac compensation problems. Their data were compared to those of patients in the cisplatin/vinorelbine group, who had only two risk factors. Considering the fact that carboplatin has a generally low rate of renal toxicity and that both schedules produced relatively good results in all of these patients, we have exclusively used carboplatin/vinorelbine since 2002.

Conclusion

In summary, it can be said that the median survival time of 17 months for our overall population and for the subgroup of patients with stage III NSCLC is an excellent result compared with radiotherapy alone, even in patients in good general health (9–12 months), but especially in patients in a reduced general condition. The survival time and the local rate of tumor control of nearly 50% support the results of a wide range of the phase II and III studies on concurrent radiochemotherapy [2, 3, 8, 11]. Our results were comparable to those of other investigators who used various platinum salt plus vinorelbine schedules (see Table 3). We think it unlikely that sequential radiotherapy-chemotherapy might achieve better results, especially since the duration of concurrent radiochemotherapy is 6–8 weeks compared to at least 14 weeks for the sequential schedule. Considering the fact that most patients receive a palliative therapy in the end, concurrent radiochemotherapy could offer them a better quality of life.

References

1. Belani C. Combined modality therapy for unresectable stage III non-small cell lung cancer. Chest 2000;117:127S–32S.
2. Choy H, Safran H, Akerley W, et al. Phase II trial of weekly paclitaxel and concurrent radiation therapy for locally advanced non-small cell lung cancer. Clin Cancer Res 1998;4:1931–6.
3. Curran W, Scott C, Langer C, et al. Phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer: initial report of Radiation Therapy Oncology Group (RTOG) 9410. Proc Am Soc Clin Oncol 2000;19:abstract 484.
4. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. J Natl Cancer Inst 1996;88:1210–5.
5. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990;323:940–5.
6. Fietkau R. Concomitant radiochemotherapy of advanced non-small-cell lung cancer. Lung Cancer 2001;33:Suppl 1:S65–76.
7. Fietkau R, Sauer R. Die frühzeitige Radiotherapie im Rahmen der Radiochemotherapie des kleinzelligen Bronchialkarzinoms ist im Stadium "Limited Disease" der späteren Bestrahlung überlegen. Strahlenther Onkol 2002;178:585–8.
8. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692–9.
9. Jeremic B, Shibamoto Y, Acimovic L, et al. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. J Clin Oncol 1995;13:452–8.
10. Jeremic B, Shibamoto Y, Acimovic L, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. J Clin Oncol 1996;14:1065–70.
11. Jeremic B, Shibamoto Y, Milicic B, et al. Concurrent radiochemotherapy for patients with stage III non-small cell lung cancer (NSCLC): long term results of a phase II study. Int J Radiat Oncol Biol Phys 1998;42: 1091–6.
12. Jeremic B, Shibamoto Y, Milicic B, et al. A phase II study of concurrent accelerated hyperfractionated radiotherapy and carboplatin/oral etoposide for elderly patients with stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1999;44:343–8.
13. Johnson DH. Locally advanced unresectable non-small-cell lung cancer: new treatment strategies. Chest 2000;117:Suppl 1:123S–6S.
14. Kisohara A, Simizu T, Uehara N, et al. Phase II study of navelbine (NVB)-cisplatin (CDDP) combination chemotherapy with concurrent radiation in non-small cell lung cancer. Proc Am Soc Clin Oncol 2001;20:abstract 2711.
15. Komaki R, Scott C, Ettinger D, et al. Randomized study of chemotherapy/radiation therapy combinations for favorable patients with locally advanced inoperable non-small cell lung cancer: Radiation Therapy Oncology Group (RTOG) 92-04. Int J Radiat Oncol Biol Phys 1997;38:149–55.
16. Lanfranco C, Testore F, Galliano M, et al. Concomitant chemoradiation therapy with carboplatin and vinorelbine in non-small-cell lung cancer (NSCLC). Low toxicity and active treatment. Presented at the 9th International Congress on Anti-Cancer Treatment (SOMPS), Paris; Feb. 2–5, 1999: 150.abstract 074.
17. Lau DH, Ryu JK, Gandara DR, et al. Concurrent carboplatin, etoposide and thoracic radiation for poor-risk stage III non-small-cell lung carcinoma: a pilot study. Int J Radiat Oncol Biol Phys 1997;38:157–61.
18. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 1991;83:417–23.
19. Le Chevalier T, Arriagada R, Tarayre M, et al. Significant effect of adjuvant chemotherapy on survival in locally advanced non-small-cell lung carcinoma. J Natl Cancer Inst 1992;84:58.
20. Marnitz S, Stuschke M, Bohsung J, et al. Intraindividual comparison of conventional three-dimensional radiotherapy and intensity modulated radiotherapy in the therapy of locally advanced non-small cell lung cancer. Strahlenther Onkol 2002;178:651–8.
21. Movsas B, Scott C, Sause W et al. The benefit of treatment intensification is age and histology-dependent in patients with locally advanced non-small cell lung cancer (NSCLC): a quality adjusted survival analysis of Radiation Therapy Oncology Group (RTOG) chemoradiation studies. Int J Radiat Oncol Biol Phys 1999;45:1143–9.

22. Perez C, Stanley K, Rubin P, et al. A prospective randomised study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung: preliminary report by the Radiation Therapy Oncology Group. Cancer 1980;45:2744–53.
23. Rosenow EC. Lung cancer: update on screening, diagnosis, and prognosis. Consultant 1995;35:1355–71.
24. Saunders M, Dische S, Barrett A, et al. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee. Lancet 1997;350:161–5.
25. Sause WT, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000;117:358–64.
26. Sause WT, Scott C, Taylor S, et al. Phase II trial of combination chemotherapy and irradiation in non-small-cell lung cancer, Radiation Therapy Oncology Group 88-04. Am J Clin Oncol 1992;15:163–7.
27. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst 1995;87:198–205.
28. Scalliet P, Goor C, Galdermans D, et al. Gemcitabine with thoracic radiotherapy – a phase II pilot study in chemonaive patients with advanced non-small cell lung cancer. Proc Am Soc Clin Oncol 1998;17:abstract 1923.
29. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 1992;32:524–30.
30. Slanina J, Laubenberger J. CT-based study on potential mediastinal lymph node spread of patients with lung cancer. Contribution to 3-D treatment planning for adjuvant radiotherapy of the mediastinum. Strahlenther Onkol 2002;178:199–208.
31. Vokes EE, Herndon JE, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B Study 9431. J Clin Oncol 2002;20:4191–8.
32. Wulf J, Hädinger U, Oppitz U, et al. Stereotactic radiotherapy of targets in the lung and liver. Strahlenther Onkol 2001;177:645–55.
33. Zatloukal P, Petruzelka L, Zemanova M, et al. Vinorelbine plus cisplatin and concurrent radiotherapy in advanced non-small-cell lung cancer. Proc Am Soc Clin Oncol 1998;17:abstract 1947.
34. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential radiochemotherapy with vinorelbine plus cisplatin (V-P) in locally advanced non-small cell lung cancer. A randomized phase II study. Proc Am Soc Clin Oncol 2000;19:abstract 1976.
35. Zips D, Taha M, Platzbecker H, et al. Ösophagusverschluss 5 Monate nach Bestrahlung eines zentralen Bronchialkarzinoms. Strahlenther Onkol 2001; 177:367–70.

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