New Combinations of Cytotoxic Agents for Non-Small Cell Lung Cancer

Neue Kombinationen in der Chemotherapie des nichtkleinzelligen Bronchialkarzinoms

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Introduction

Taxanes and platinum derivatives are emerging as an important combination in the treatment of non-small cell lung cancer (NSCLC). The use of paclitaxel plus carboplatin has been received much attention in recent years, and there is now increasing interest in combinations of docetaxel and platinum derivatives. Recent attention has also focussed on the development of non-platinum combinations for the treatment of NSCLC.

Docetaxel and Platinum

Several phase II studies have investigated the efficacy of docetaxel (75 and 100 mg/m²) and cisplatin in chemotherapy-naïve patients with NSCLC. Response rates were encouraging and ranged from 32 to 52% [1–8] (table 1). Similarly, in phase II studies the combination of docetaxel (65 and 100 mg/m²) and carboplatin have shown response rates of 25–67% [9–16] (table 2). The most impressive results originate from a study by Herse et al. [11] who used a regimen of docetaxel, 100mg/m² and carboplatin, AUC = 7.5, as neoadjuvant therapy in patients with stage IIIB disease and achieved a response rate of 67%, following 4 cycles of chemotherapy.

The results of the ongoing Tax 326 trial are eagerly awaited. In this trial three regimens are under investigation, docetaxel plus cisplatin, docetaxel plus carboplatin, and vinorelbine plus cisplatin. This study will help to determine whether a difference exists between cisplatin and carboplatin in terms of efficacy and survival. In addition, the results will provide an indication of whether combinations of docetaxel plus platinum derivatives are superior to the combination of vinorelbine plus cisplatin.

The recently reported Eastern Cooperative Oncology Group Study 1594 [17] evaluated the outcome of four combination regimens in the treatment of advanced NSCLC: paclitaxel/cisplatin, docetaxel/cisplatin, gemcitabine/cisplatin, and paclitaxel/carboplatin. No differences in the primary endpoint of survival were observed, and no regimen emerged as a true standard treatment for advanced NSCLC.

Docetaxel and Gemcitabine: Phase I

In a phase I study performed by Rizvi et al. [18], the combination of docetaxel and gemcitabine was evaluated in 34 patients with advanced NSCLC. These two agents have shown excellent single-agent activity in pretreated and untreated NSCLC [19, 20]. Furthermore, the risk of neuropathic and myalgic side effects is lower with docetaxel than paclitaxel, and therefore docetaxel was selected in this study. Both gemcitabine and docetaxel were given on days 1 and 8 every 21 days. In one arm gemcitabine was immediately followed by docetaxel; in the other arm docetaxel was followed by gemcitabine. A 5-step dose-escalating regimen was used, starting from 30 mg/m² docetaxel and 800 mg/m² gemcitabine, with a maximum dose of 50 mg/m² and 1,250 mg/m², respectively. No growth factor support was used, at least during the 1st cycle of therapy. The results showed that only untreated and minimally pretreated patients (i.e. no more than 1 previous episode of chemotherapy) tolerated the higher dose levels (40 mg/m² or 50 mg/m² docetaxel plus 1,250 mg/m² gemcitabine). The two arms were comparable in terms of drug levels and the incidence of toxicity. As expected, the most common toxicity was grade 3/4 neutropenia, which was observed in 7 out of 34 (21%) patients although this side effect was not observed in the minimally pretreated patients (n = 19). No clinically significant fluid retention, neuropathy, or myalgia was observed. These findings suggest that, for phase II studies, the recommended dose levels of docetaxel and gemcitabine in heavily pretreated patients are 30 mg/m² and 800 mg/m², respectively, administered intravenously on days 1 and 8 and repeated every 3 weeks. In minimally pretreated or untreated patients recommended doses are 40 mg/m² and 1,000 mg/m², respectively, administered intravenously on days 1 and 8 and repeated every 3 weeks.

Docetaxel and Gemcitabine: Phase II

Spiridonidis et al. [21] performed a phase II study in 40 pretreated patients with measurable advanced NSCLC who had

Table 1. Efficacy of combination therapy with docetaxel plus cisplatin: Phase II studies [mod. after Rizvi]

Reference	Docetaxel, mg/m ²	Cisplatin, mg/m ²	Number of patients	Response rate, %	Median survival time, months
Le Chevalier et al., 1998 [1]	75	100	51	33	8.4
Zalcberg et al., 1998 [2]	75	75	47	39	9.6
Belani et al., 1999 [3]	75	75	47	32	11.3
Faderl et al., 1998 [4]	75	75	53 (47 eval.)	40	n.r.
Cole et al., 1997 [5]	65	100	10	50	> 9
	75	75	25	52	> 10
Androulakis et al., 1997 [6]	100	75	52 (49 eval.)	47	6.0
Georgoulas et al., 1998 [7]	100	80	53	45	13.5
Takeda et al., 2000 [8]	60	80	53 (44 eval.)	41	8.0

n.r. = Not reported; eval. = evaluated for response.

Table 2. Response rates and principal adverse events of combined therapy with docetaxel plus carboplatin [mod. after Rizvi]

Reference	Docetaxel, mg/m ²	Carboplatin (AUC), mg/ml/min	Number of patients	Response rate, %	Principal adverse event
Schütte et al., 2000 [9]	90	5	30	30	N
Capozzoli et al., 1998 [10]	80	6	27	48	N, FN
Herse et al., 1998 [11]	100	7.5	15 (9 eval.)	67	N, FN
Millward et al., 1999 [12]	75	6	45	37	N, FN
Harvey et al., 2000 [13]	80	6	20	55	N
Jahanzeb et al., 2000 [14]	80	6	25 (20 eval.)	35	N
Arcenas et al., 2000 [15]	65	6	20	41	N
West et al., 2000 [16]	65	6	40 (36 eval.)	25	N

N = Neutropenia; FN = febrile neutropenia; eval. = evaluated for response.

Table 3. Hematological toxicities associated with docetaxel plus gemcitabine in 40 pretreated patients with advanced NSCLC [mod. after 21]

Toxicity	Patients	
	n	%
<i>Neutropenia</i>		
Grade 4	21	53
With fever	4	10
<i>Anemia</i>		
PRBC transfusion	9	23
<i>Thrombocytopenia</i>		
Grade 3/4	8	20
Platelet transfusion	4	10

failed at least one chemotherapy regimen. Subjects had a SWOG performance status of 0–2 and no prior exposure to taxanes or gemcitabine. Following the results of an earlier phase I study [22], docetaxel was administered at a dose of 100 mg/m² on day 1 plus gemcitabine 800 mg/m² on days 1, 8 and 15. Treatment was repeated every 4 weeks, with no routine

granulocyte colony stimulating factor (G-CSF) support. The majority of patients had received previous chemotherapy with a platinum agent plus vinorelbine (n=26); platinum and etoposide had been used in 10 patients. The remaining 4 patients had received monotherapy with a non-platinum agent. In around half of the patients (21/40) grade 4 neutropenia was reported, and about a quarter of the population (9/40) required red blood cell or platelet transfusions (table 3). The most frequent nonhematological toxicity was asthenia which occurred in around one third (13/40) of patients (table 4). Of the 38 patients who were evaluable for response, a response rate of 32% was observed, with a median response duration of 8 months. Another phase II study performed by Rebattu et al. [23] evaluated a 3-week regimen of docetaxel 85 mg/m² (day 8) plus gemcitabine 1,000 mg/m² (days 1 and 8) in 36 patients with advanced NSCLC who had received no more than one previous episode of chemotherapy. Similar findings to those observed in the study of Spiridonidis et al. [21] were reported. Grade 3/4 neutropenia was the major toxicity, occurring in half of the patients studied (18/36). The overall response rate in all treated patients was 30%, and after a median follow-up period of 7.9 months, projected 1-year survival rate was 35%.

Table 4. Grade 3 nonhematological toxicities associated with docetaxel plus gemcitabine in 40 pretreated patients with advanced NSCLC [mod. after 21]

Toxicity	Patients	
	n	%
Asthenia	13	33
Edema	4	10
Vomiting	3	8
Flu-like symptoms	1	3
Mucositis	1	3
Diarrhea	1	3
Elevated transaminases	1	3

Table 5. Efficacy docetaxel/cisplatin versus docetaxel/gemcitabine [mod. after 24]

	Docetaxel/ cisplatin	Docetaxel/ gemcitabine
Patients treated/evaluated	152/132	144/114
Complete responses (%)	3 (2.3)	1 (0.9)
Partial responses (%)	39 (30)	38 (33)
Overall response rate (95% CI), %	32 (24–48)	34 (25–43)
Stable disease (%)	42 (32)	37 (32)
Progressive disease (%)	48 (36)	38 (33)
Duration of response, months	5	4
Time to progression, months	8	8
Median survival, months	10	9
1-year survival rate, %	42	38

Georgoulas et al. [24] performed a randomized trial comparing a regimen of docetaxel (100 mg/m² on day 1) plus cisplatin (80 mg/m² on day 2) with docetaxel (100 mg/m² on day 8) plus gemcitabine (1,100 mg/m² on days 1 and 8) in 315 previously untreated patients with advanced NSCLC (fig. 1). Treatment was repeated every 3 weeks, and prophylactic G-CSF was administered. The incidence of toxicities was comparable in the two treatment arms, apart from grade 3/4 diarrhea which was observed more frequently in the docetaxel/cisplatin arm than the docetaxel/gemcitabine arm (12% versus 3%, $p=0.003$). The overall response rates were similar in the two treatment arms (32% and 34%, respectively), and other efficacy parameters were also comparable (table 5).

Other New Combinations

Another combination regimen that is under investigation for advanced NSCLC is gemcitabine plus irinotecan. This combination is currently being evaluated in a phase II study conducted by Cancer and Leukemia Group B. In this study, chemotherapy-naïve patients with stage IIIB/IV tumors and performance status 0–1 will receive gemcitabine (1,000 mg/m²) plus docetaxel (40 mg/m²) or irinotecan (100 mg/m²) in a regimen that is repeated every 3 weeks.

Fig. 1. Comparison of combination therapy with docetaxel/cisplatin (DC) or docetaxel/gemcitabine (DG) in patients with advanced NSCLC: Study design [mod. after 24].

Another interesting combination is that of vinorelbine plus docetaxel. In phase I studies, where significant myelosuppression was observed, a 2-weekly schedule of 45 mg/m² vinorelbine and 60 mg/m² docetaxel was recommended for phase II trials [25]. This regimen has recently been investigated in chemotherapy-naïve patients with advanced NSCLC [26]. Patients also received prophylactic treatment with dexamethasone, G-CSF, and ciprofloxacin. After a median follow-up time of 14 months, the objective response rate was 51%, the predicted median survival time 14 months and the 1-year survival rate 60%. Febrile neutropenia was observed in only 5 patients and in 5 (1.3%) of the 384 cycles of treatment. The prophylactic use of G-CSF and the 2-week schedule permitted a single-agent dose intensity of both drugs to be achieved in this study. Cumulative toxicities such as nail changes, lacrimation, and fatigue were observed after several months of treatment and limited the duration of therapy. The authors concluded that this 2-week regimen of docetaxel plus vinorelbine is highly active and may be appropriate in circumstances such as induction or postoperative chemotherapy where brief, fixed periods of treatment are required.

Conclusion

The significant toxicity of traditional platinum-based regimens used in the treatment of advanced NSCLC has led to the search for alternatives in combination chemotherapy. During the last decade, there has been a rapid increase in the number of agents with proven activity in NSCLC of which gemcitabine plus docetaxel is one of the most promising new combinations. When combined, both can be given at nearly full single-agent doses with favorable toxicity profile and efficacy in previously treated and untreated patient populations. Furthermore, in untreated patients with advanced NSCLC this combination has shown comparable efficacy to the combination of docetaxel plus cisplatin. Further research is necessary to determine the role of these combinations in the management of advanced

NSCLC, including their use in the adjuvant and neoadjuvant settings. Other new combinations with significant activity are currently being evaluated, including the addition of biological agents such as bcl-2 antisense compounds to various chemotherapeutic regimens.

Summary

At present, there is no accepted standard chemotherapeutic regimen for the first-line treatment of advanced NSCLC, and a

wide range of regimens are under investigation. The significant toxicity of traditional cisplatin-based regimens has led to the evaluation of alternative chemotherapeutic regimens that are active in NSCLC. The last decade has seen a rapid increase in the number of agents with proven activity in NSCLC, including docetaxel, gemcitabine and vinorelbine. Current evidence suggests that combinations of docetaxel plus gemcitabine or vinorelbine are active and well tolerated in patients with advanced NSCLC. Further research is warranted to establish the place of these combinations in the management of this disease, including their role in the adjuvant and neoadjuvant settings.

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