Docetaxel as a Single Agent in First-Line Therapy of Non-Small Cell Lung Cancer

Docetaxel als Monosubstanz in der First-line-Therapie des kleinzelligen Bronchialkarzinoms

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Phase II Studies Show Impressive Results

Originally, 4 phase II studies were performed using docetaxel in first-line chemotherapy of non-small cell lung cancer (NSCLC). The dose applied was 100 mg/m² over 1 h every 3 weeks, which was found to be reasonably safe in phase I studies. Patients with stage IV or unresectable stage III NSCLC, who had no prior chemotherapy and with a WHO performance status of 2 or less, were eligible. The patients received no prophylactic anti-emetic treatment or G-CSF support and – most important – no prophylactic corticosteroids. This in turn leads to pleural effusions, peripheral edema, and hematological side effects as shown in table 1.

Altogether, 160 patients were treated and 128 could be evaluated. 69% of the population were male and 79% had stage IV disease. The performance status was 1 in the majority of patients (58%), 0 in 25% and 2 in 17% of patients. The results of these studies were quite impressive. For instance, in the study of Fossella and coworkers [1] a median survival of 47 weeks and a 1-year survival rate of 45% was achieved.

Among other phase II studies performed later, a Japanese study [2] seems to be interesting. In this study, a dose of 60 mg/m² docetaxel was applied in 167 patients. The authors reported no significant toxicity, which apparently was due to the dose modification. In spite of the low dose, the median survival time was 42 weeks and the 1-year survival rate was 41%.

TAX 308, a Pivotal Study

Recently the pivotal phase III study (TAX 308) of docetaxel versus best supportive care in first-line treatment of NSCLC was performed in 207 patients [3]. Docetaxel was applied at a dose of 100 mg/m². This study demonstrated for the first time, that a single agent improved median survival significantly. The magnitude of the difference in favor of docetaxel was comparable with survival benefits induced by cisplatin combination regimens according to a meta-analysis.

Mechanisms of Resistance

Tubulin is a natural target of antimitotic drugs, for example for depolymerizing or tubulin-stabilizing agents such as the taxanes. Mutations of beta-tubulin may be crucial for the interaction between docetaxel and tubulin. In mutant cells these agents have reduced activity.

Taxanes bind to specific amino acids coded at the beginning of exon 1 and even more important of exon 4 of the tubulin gene. Last year, we could demonstrate that at least one third of NSCLC patients receiving paclitaxel as a single agent had different missense mutations on exon 4. In these paclitaxel-resistant cells containing tubulin mutations we also found p53-mutations. It is in the focus of interest, whether these p53-mutations confer resistance to taxanes. However, recent experiments support the observation, that resistance to taxanes might be independent of p53.

One of the mechanisms by which taxanes induce mitotic arrest is the increased phosphorylation of raf-1 kinase and bcl-2. Tumor cells overexpressing bcl-2 therefore could be more sensitive to taxanes. In fact, prostate cancer cells expressing bcl-2 were more paclitaxel-sensitive than others. So, reduced phosphorylation of bcl-2 could be an important mechanism of resistance against taxanes. Docetaxel has been found to be 100 times more potent than paclitaxel in promoting bcl-2 phosphorylation, when used at the usual concentrations. At low concentrations paclitaxel has been shown to induce apoptosis by a raf-independent pathway. In sensitive cell lines paclitaxel induced a high phosphorylation of raf-1 or bcl-2, while p53 was not expressed. This supports the hypothesis that p53 mutations do not play a role in taxane resistance.

A Rationale for Sequential Therapy

In fact, the opposite seems to be true. Microtubule-associated proteins which enhance the tubulin-stabilizing action of taxanes, are overexpressed in tumors with non-functional p53. This could be a rationale for sequential chemotherapy using cispla-

Table 1. Phase II studies of Docetaxel in first-line therapy of NSCLC (mod. after Rosell)

Author	Patients evaluable	Response							Median duration of response	
		complete		partial		overall		95% C.I.	weeks	range
		N	%	N	%	N	%			
Cerny	35	1	3	7	20	8	23	10–40	36	15–48
Burris	38	0	0	12	32	12	32	18–49	25	24–48
Francis	29	0	0	9	31	9	31	n.r.	23	10–43+
Fossella	39	0	0	13	33	13	33	n.r.	14	5+–49+

tin combinations first, followed by taxanes. DNA-damaging agents would induce p53 mutations, and taxanes could be more effective when administered thereafter. The phase II SWOG 9806 trial [4] will test this hypothesis comparing gemcitabine/carboplatin followed by paclitaxel in one arm with vinorelbine/cisplatin followed by docetaxel in the second arm.

Conclusion

Docetaxel is an active drug in advanced NSCLC patients. Single-agent response rate in first-line setting is about 30% at a dose of 100 mg/m² every 3 weeks; equivalent responses may be seen at lower doses (60–75 mg/m²). Molecular analysis howed that p53 mutations induced by DNA-damaging agents can enhance the activity of taxanes.

References

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