Strahlentherapie
und Onkologie

Originalarbeit

Combined Radiochemotherapy with Docetaxel in Patients with Unresectable Locally Advanced Head and Neck Tumors

Katja Hesse[1], Bernhard Heinrich[1], Frank Zimmermann[1], Reinhard Kau[2], Gabriele Sommer[3], Wolf Achterrath[3], Michael Molls[1], Horst Jürgen Feldmann[1]

Background: As the treatment with Docetaxel in metastatic head and neck cancer resulted in an encouraging response rate, the following phase-I study examined the effects of a combined radiochemotherapy with weekly Docetaxel in patients with inoperable advanced head and neck tumors.
Patients and Methods: Six patients with Stage IV head and neck cancer were included into the study. Within the treatment regimen the primary tumor and the involved lymph nodes were irradiated up to a total dose of 70 Gy, the non involved cervical and supraclavicular lymph nodes received 50 Gy in conventional fractionation. Simultaneously Docetaxel was given 1 hour before radiotherapy. The initial dose was 15 mg/m^2.
Results: A dose escalation was impossible because of several dose limiting toxicities (NCI-CTC) already in the first dose level. Two patients showed skin reactions Grade 4, 2 patients pulmonary complications Grade 4, 2 patients neurologic side effects Grade 3 and 1 a thrombocytopenia Grade 3. The response rate resulted in 3 complete and 1 partial remission, 1 death, 1 patient was not evaluable.
Conclusion: Unexpectedly already in the first dose level several dose limiting toxicities were evaluated. For that reason the treatment scheme is not feasible.

Key Words: Radiochemotherapy · Docetaxel · Head and neck tumor

Kombinierte Radiochemotherapie mit Docetaxel bei Patienten mit inoperablen fortgeschrittenen HNO-Tumoren

Hintergrund: Da die Behandlung mit Docetaxel bei metastasierten HNO-Tumoren eine günstige Ansprechrate ergeben hat, untersuchte die folgende Phase-I-Studie die Effekte einer kombinierten Radiochemotherapie mit wöchentlicher Gabe von Docetaxel bei Patienten mit inoperablen fortgeschrittenen HNO-Tumoren.
Patienten und Methoden: In der Zeit von September 1997 bis März 1998 wurden sechs Patienten mit fortgeschrittenen HNO-Tumoren im Stadium IV in die Studie eingeschlossen. Innerhalb des Therapieregimes wurden der Primärtumor und die befallenen Lymphknoten bis 70 Gy bestrahlt, die nicht befallenen zervikalen und supraklavikulären Lymphknoten erhielten 50 Gy in konventioneller Fraktionierung. Simultan wurde Docetaxel eine Stunde vor der Bestrahlung gegeben. Die initiale Dosis lag bei 15 mg/m^2.
Ergebnis: Eine Dosiseskalation war nicht möglich, da bereits im ersten Dosislevel zahlreiche dosislimitierende Toxizitäten (NCI-CTC) aufgetreten sind. Hautreaktionen Grad 4, pulmonale Komplikationen Grad 4 sowie neurologische Nebenwirkungen Grad 3 zeigten sich bei je zwei Patienten und bei einem Patienten eine Thrombozytopenie Grad 3. Die Ansprechrate ergab drei komplette und eine partielle Remission, einen Todesfall, ein Patient war nicht auswertbar.
Schlußfolgerung: Unerwarteterweise sind bereits im ersten Dosislevel zahlreiche dosislimitierende Komplikationen aufgetreten, so daß die Behandlung so nicht durchführbar ist.

Schlüsselwörter: Radiochemotherapie · HNO-Tumoren · Docetaxel

[1]Klinik für Strahlentherapie und Radiologische Onkologie und
[2]HNO-Klinik, Klinikum rechts der Isar der TU München,
[3]Rhone-Poulenc Rorer, Köln.

Submitted: 26 July 1999.
Accepted: 6 Dec 1999.

Despite many attempts to improve outcome of advanced head and neck tumors the 5-year survival remains about 20 to 30% [8, 13, 28]. Most of these patients die from local recurrences, while up to 30% develop distant metastases. Ten to 20% suffer from a second tumor, usually elsewhere in the head and neck area or in the bronchus or esophagus [23]. Many clinical trials testing simultaneous chemoradiotherapy versus conventional radiotherapy alone showed a modest benefit in terms of response and survival for the combined modality treatment [16, 26, 35], the most effective of them with 5 FU and platin improved the 5-year survival rate about 12% [13]. In contrast induction chemotherapy schemes have not achieved a significant improvement of survival [8, 13, 26, 29] but have still a role in laryngeal preservation. Also hyperfractioned and accelerated application of radiotherapy so far have not presented better results than combined chemoradiation [1, 2, 12]. The efficacy of hyperfractioned radiation and simultaneous chemotherapy is still in evaluation [14]. First results showed an encouraging 5-year survival of 37% [23], although the rate of acute toxicity is considerably higher in hyperfractioned treatment schemes [27].

Inclusion of new cytotoxic drugs into chemoradiation might improve results. One of the most promising drugs is Docetaxel. The overall response in phase-II trials in the treatment of recurrent disease in head and neck tumors using Docetaxel in a dose of 100 mg/m^2 every 3 weeks was up to 42% [9, 22, 30], while carbo-/cisplatin reached only a response rate of 20 to 30% [19]. In addition to the direct cytotoxic action of taxanes, several studies described a radiosensitizing effect of the taxanes in vitro [6, 18, 32]. This might be the reason for the promising response rate of chemoradiation with taxanes in different entities like the bronchus carcinoma [5, 19, 24]. Therefore we initiated a phase-I trial with Docetaxel in a combined chemoradiotherapy for advanced head and neck tumors. Primary objective of this phase-I study was the definition of the maximal tolerable dose, the recommended dose and dose limiting toxicities. Secondary objectives were response rate and duration.

Patients and Methods

Patients: The criteria for inclusion and exclusion of patients in the study are listed in Table 1.

Treatment Regimen: Head and neck irradiation: The treatment consisted of a total tumor dose of radiation of 70 Gy for the primary tumor and involved lymph node areas. It was applied as a dose of 2 Gy daily on days 1 to 5 during 7 weeks. Radiation was performed by a megavolt linear accelerator (6 MeV). The treatment volume included the primary tumor and the clinically involved lymph nodes. For the cervical and supraclavicular lymph node areas without clinical involvement the total tumor dose was 50 Gy. The spinal cord was shielded after 30 Gy. On days of chemotherapy radiation was given 1 hour after completion of the Docetaxel short-time infusion.

Chemotherapy: On days 1, 8, 15, 22, 29, 36, 43 Docetaxel was given intravenously in 1 hour. To avoid allergic reactions and fluid retention patients received dexamethason (2 times 8 mg per day) 1 day prior to until 1 day after chemotherapy. The starting dose was 15 mg/m^2 and escalation was planned in steps of 5 mg/m^2, if 3 of 3 or at least 4 of 6 patients do not show any dose limiting toxicity.

Dose limiting toxicities were defined as mucositis Grade 4 and skin side effects Grade 4 lasting up to the next infusion date of Docetaxel, neurological symptoms Grade 3, irreversible renal and hepatic disorders, thrombocytopenia Grade 3 and/or granulocytopenia Grade 4 for more than 3 days, as described in NCI Common Toxicity Criteria. The application of G-CSF was not allowed within the study.

The study was approved by the local ethics committee. Therapy was given with best supportive care including close observation on the ward.

Follow-Up: Four and 12 weeks after finishing treatment late side effects and response were documented by clinical examination, taking biopsies, magnetic resonance of the head and neck, chest X-ray and ultrasound abdomen. After that the follow-up was repeated every 3 months.

Results

Between September 1997 and March 1998 6 patients (5 male, 1 female) with a median age of 52 years (34 to 67 years) were included in the study. All patients suffered from a Stage IV head and neck tumor (Table 2). Two patients followed the treatment plan without complications. Another patient finished the treatment regimen as well. However, the application of chemotherapy had to be delayed because of a thrombocytopenia Grade 3 during simultaneous treatment with fluconazol (Diflucan®) and metamizol (Novalgin®). Further 3 patients could not pass all cycles of chemotherapy, 1 of them also had to stop the irradiation in the second half of the treatment plan. Reasons for that consisted of numerous unexpected dose-limiting toxicities.

Inclusion criteria	Exclusion criteria
Measurable and evaluable tumor	Presence of distant metastases
Age between 18 and 70 years	Prior treatment with corticosteroids within 30 days
WHO-performance status ≤ 2	Pregnancy
Life expectancy of at least 3 months	Ascites or pericardial or pleural infusion
Signed informed consent prior to beginning the treatment	Preexisting renal, cardial, pulmonary, hepatic, neurological, psychiatric disease
Histologically confirmed head and neck cancer	Active infection
Creatinine clearance ≥ 60 ml/min	Prior participation in another study within 30 days
	Prior treatment to the head and neck tumor
	Prior malignancy besides non melanoma skin cancer or excised cervical carcinoma in situ

Table 1. In- and exclusion criteria of the phase-I study with Docetaxel and radiotherapy for advanced head and neck tumors.

Tabelle 1. Ein- und Ausschlußkriterien der Phase-I-Studie mit Docetaxel und Bestrahlung bei fortgeschrittenen HNO-Tumoren.

Pat.-No.	Age (years)	Localization of tumor	Stage (all M0)	Irradiation	Chemotherapy 15 mg/m^2 weekly	Dose-limiting toxicity, Grade	Diagnostics	Response 4–8 weeks after RCTx	Follow-up	Outcome
1	42	Base of tongue, infiltration in mandibula	cT4 N2b G2	70 Gy	5 cycles	Urine retention 3 (interpreted neurologically)	MRI, liquor	CR	2 months	Bone metastases, lung cancer
2	34	Tonsil, uvula, nasopharynx	cT4 N1 G3	70 Gy	7 cycles	None		PR	6 months	Local CR, pulmonary, hepatic met.
3	50	Base of tongue	cT4 N2b G2	70 Gy	7 cycles	Thrombopenia 3	During Diflucan® + Novalgin®	CR	17 months	Stable
4	56	Base of tongue, epiglottis	cT4 N1 G2	54 Gy	6 cycles	Pneumonia of aspiration 4, skin ulceration 4	Radiologically proven	Section: necrosis of tumor	3 weeks	Death, Staph. aureus sepsis
5	53	Tonsil, base of tongue	cT4 N2 G2	70 Gy	4 cycles	Peroneal paralysis 3, hypesthesia 2	MRI, liquor, EMG	CR	12 months	Stable
6	67	Tonsil, palate	cT3 N3 G3	70 Gy	7 cycles	Pneumonia of aspiration 4, skin ulceration 4	Radiologically proven, bronchoscopy	PD	2 months	Death: suspected lung embolism

Table 2. Results: Survey of each participating patient in phase-I study with weekly Docetaxel and simultaneous radiotherapy.

Tabelle 2. Therapieergebnisse: Übersicht über jeden teilnehmenden Patienten an der Phase-I-Studie mit wöchentlicher Gabe von Docetaxel und simultaner Strahlentherapie.

Dose-Limiting Toxicities (Table 2): Two patients developed a neurologic symptomatology Grade 3, 1 as a repeated reversible retention of urine which disappeared under spasmolytic treatment with carbachol and 1 as peroneal paralysis Grade 3 which were reversible after months of physiotherapeutic treatment. Despite intensive examinations including MRI of the central nervous system, examination of liquor and urologic tract no further explanations as a toxic reaction to Docetaxel were found for these both symptoms. Two patients showed an exulcerating dermatitis Grade 4 which was interpreted as a radiosensitizing effect of Docetaxel. The same 2 patients also experienced a pneumonia Grade 4 most probably caused by aspiration. Radiologically both had a disorder in swallowing. However, different reasons as an atypical pneumonia without finding pathological bacteria or as an interstitial pneumonia caused by Docetaxel could not be excluded for sure.

Mucositis Grade 3	6/6
Skin	
Grade 1	1/6
Grade 2	2/6
Grade 3	1/6
Infection	
Grade 1	2/6
Grade 2	1/6
Fever without infection	
Grade 1	2/6
Grade 2	1/6
GPT	
Grade 1	1/6
Grade 2	1/6
Edema Grade 2	2/6
Diarrhea Grade 1	1/6
Nausea Grade 2	1/6
Neuropathy Grade 1	1/6
Weight loss	
Grade 1	2/6
Grade 2	1/6
Anemia	
Grade 1	2/6
Grade 2	3/6
Lymphocytopenia	
Grade 3	2/6
Grade 4	4/6

Table 3. Results: Non-dose limiting side effects of phase-I study with Docetaxel and radiotherapy for advanced head and neck tumors.

Tabelle 3. Therapieergebnisse: Nicht dosislimitierende Nebenwirkungen der Phase-I-Studie mit Docetaxel und Strahlentherapie bei fortgeschrittenen HNO-Tumoren.

Non-Dose Limiting Toxicities: A mucositis Grade 3 and erythema Grade 1 were observed in all patients. Nobody developed a leuko-/neutropenia or anemia, however, everybody showed a severe lymphopenia at least during week 4 to 6 of treatment. Further side effects are listed in Table 3.

Response and Follow-Up: Three patients had a complete remission, 1 patient achieved a partial remission. Two of them developed metastatic disease (see Table 2). Two patients could not be evaluated because of their early deaths after treatment. Both showed a clinical response first. One patient died 4 weeks later within a progressive disease probably by pulmonary embolism. An autopsy of the second patient described a necrotic destruction of the tumor including the glottis.

Discussion

Docetaxel showed an encouraging cytotoxic activity in the treatment of patients with advanced head and neck tumors

in the first and second line therapy [3, 4, 9, 11, 30]. Beside of that several studies described a radiosensitizing effect of the taxanes in vitro [18, 32]. The mechanism of the taxanes is based on the stabilization of the microtubules. Tissue culture studies have proven the ability of the taxanes to block and prolong cells in the G2/M phase, which is known as the most radiosensitive phase of the cell cycle [32]. So far this phenomenon could not be shown in vivo [32]. Referring to Hennequin et al. [18] the radiosensitizing effect depends on the concentration of the taxanes and differs from cell to cell line tested in vitro. Nevertheless these effects might be an explanation for the unexpected and different toxicities, we found already in the first dose level. In most phase-I/II studies with taxanes dose limiting toxicities consisted of mucositis and short lasting neutropenia. In almost all schemes the taxanes were given every 3 weeks (Table 4) [3, 7, 10, 19, 22]. Recent publications often use weekly applications, which seem to cause less neutropenia [17, 21, 24]. Without radiotherapy the recommended dose for weekly application of Docetaxel within phase-II studies is 36 mg/m^2 [17]. In combination with radiotherapy the maximal tolerated weekly dose still is not defined. Forty-two patients with postoperative (TUR) bladder carcinoma who received 68 to 74 Gy/2 Gy and cisplatin 30 mg/m^2 once a week tolerated Docetaxel 40 mg/m^2 weekly simultaneously [34]. In comparison to that another group treating patients with advanced NSCLC and esophagus carcinoma, considered a dose of 20 mg/m^2 as tolerable [24] (Table 5). In our study already 15 mg/m^2 weekly were dose limiting. The reason for these differences might have been unfavorable constitution of our patients caused by longstanding abuse of nicotine and alcohol which were not visible despite strict inclusion criteria. Advanced age possibly contributed to the negative outcome of the 2 oldest participating patients. As one explanation some biological and molecular data indicate a rising radiation sensitivity with growing age caused by a reduction of DNA repair mechanisms [15].

Phase-II study	Number of patients	Entity and stage	Chemotherapy with Docetaxel	Response (CR + PR) (%)	Side effects, Grade
Couteau et al. [4]	15	Advan./recur. head and neck	100 mg/m^2 4 cycles	27	Neutropenia 3–4: 73%, skin 1–2: 80%
Dreyfuss et al. [9]	31	Advan./recur. head and neck	100 mg/m^2 5 cycles	42	Neutropenia 3–4: 53%, neurotox. 3: 2/31
Fujii et al. [11]	24	Advan./recur. head and neck	60 mg/m^2 2 cycles	17.4	Neutropenia 3–4: 77%
Catimel et al. [3]	39	Advan./recur. head and neck	100 mg/m^2 4 cycles	32	Neutropenia 3–4: 61%, skin 1–2: 54%
Posner et al. [30]	28	Metast./recur. head and neck	100 mg/m^2	50	Leukopenia: 43%, mucositis 2: 4%, neurotox. 3: 1%
Fossela et al. [10]	41	NSCLC IIIB–IV	100 mg/m^2	33	Neutropenia 3–4: 97%, severe infection: 17%, skin 1–2: 74%, neuropathy 1: 37%

Table 4. Comparison of response and side effects of phase-II studies with Docetaxel applicated every 3 weeks/no irradiation in advanced tumors.

Tabelle 4. Vergleich der Ansprechraten und Nebenwirkungen von Phase-II-Studien mit Docetaxel in dreiwöchentlichem Rhythmus/keine Bestrahlung bei fortgeschrittenen Tumorerkrankungen.

Author	Number of patients	Entity and stage	Radiotherapy 2 Gy/fraction	Chemotherapy	Dose limiting toxicity	Side effects, Grade
Hainsworth et al. [17]	38	Advan./refract. malignancies	None	Docetaxel	43 mg/m^2	Fatigue and asthenia
Maurer et al. [24]	27	NSCLC, esophagus	60 Gy	Docetaxel	25 mg/m^2	Esophagitis/pulmonary
Hoffmann et al. [21]	18	Advan. head and neck	60–70 Gy	Paclitaxel	30 mg/m^2	Mucositis 4
Choy et al. [5]	27	Advan. NSCLC	60 Gy	Paclitaxel	70 mg/m^2	Esophagitis 4, neutropenia 3
Varveris et al. [34]	42	Bladder carcinoma post TUR	68–74 Gy	Cisplatin 30 mg/m^2, Docetaxel	40 mg/m^2	Neutropenia 3–4: 8%, stricture of bladder: 4/37, paresthesia: 3/37, mot. dysfunction: 1/37

Table 5. Comparison of dose-limiting toxicities of phase-I/II studies with combined radiochemotherapy and weekly application of taxanes.

Tabelle 5. Vergleich der dosislimitierenden Toxizitäten von Phase-I/II-Studien mit kombinierter Radiochemotherapie und wöchentlicher Applikation von Taxanen.

The responsible toxicities as severe cutaneous, neurologic and pulmonary side effects have been seen rarely in published studies. The exulcerating dermatitis was interpreted as a radiosensitizing effect of Docetaxel. For neurologic side effects probabilities of up to 50% of mild neuropathy as well as 14% motoric disorders have been described. Severe neuropathy has occurred especially after cumulative dosage over 600 mg/m^2 [20, 33]. In our study only a maximal dosage of 105 mg/m^2 was applied. Possibly the patients were more sensible, as they already had latent neurologic defects caused by usually intensive nicotin and alcohol consumption. Another reason might be an enhanced damage of nerves (including vagal nerve) passing through the irradiation area due to the radiosensitizing effect of Docetaxel, although the dose applied to the myelon was limited to 30 Gy.

Referring to the pulmonary complications in our study the most probable reason of the pneumonia is aspiration. Nevertheless an interstitial pneumonia outside the radiation field, which is known as a rare toxic effect of the taxanes, could not be excluded as an additional component. As a potential reason for this reaction a disorder of the T-cell immune system is suspected [25]. In the study of Reckzeh et al. [31] 7 of 14 patients with inoperable lung cancer treated with paclitaxel in a weekly dose of 50 to 86 mg/m^2 during simultaneous radiotherapy developed a moderate to severe interstitial pneumonia outside the irradiated area. During treatment all 14 patients presented a severe lymphocytopenia. In our study 2 out of 6 patients showed pulmonary complications and all patients passed a severe lymphocytopenia at least during 3 weeks of treatment. In contrast Merad et al. [25] reported 2 cases of interstitial pneumonia without lymphocytopenia after standard chemotherapy with Docetaxel in a dose of 100 mg/m^2 every 3 weeks. In summary it might be possible, that the risk for Docetaxel-induced interstitial pneumonia is increased by simultaneous lymphocytopenia and that weekly application of Docetaxel more often induces lymphopenia than the standard dosage. Dexamethasone, which was used prophylactically in our study, might have contributed to this phenomenon. The exact correlation between these both symptoms so far remains open.

Conclusion

Already in the first dose level of weekly Docetaxel parallel to radiation therapy of head and neck tumors several dose limiting toxicities were evident. Instead of the expected mucositis and neutropenia this study had to be stopped because of pulmonary, cutaneous and neurologic side effects. Therefore, despite the high activity of Docetaxel used as a cytostatic drug alone, its inclusion in simultaneous radiochemotherapy of head and neck tumors is problematic. Before routinely used in this setting, further work with other dosing schedules has to be performed.

References

1. Antognoni P, Bignardi M, Cazzaniga LF, et al. Accelerated radiation therapy for locally advanced squamous cell carcinomas of the oral cavity and oropharynx selected according to tumor cell kinetics- a Phase II multicenter study. Int J Radiat Oncol Biol Phys 1996;36:1137–45.
2. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798–804.
3. Catimel G, Verweij J, Mattijssen V, et al. Docetaxel (Taxotere): An active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. Ann Oncol 1994;5:533–7.
4. Couteau C, Leyvraz S, Oulid-Aissa D, et al. A phase II study of docetaxel in squamous cell carcinoma (SCC) of the head and neck (ENG). Proc Am Soc Clin Oncol 1996;15:315.
5. Choy H, Akerley W, Safran H, et al. Phase I trial of outpatient weekly paclitaxel and concurrent radiation therapy for advanced non-small-cell lung cancer. J Clin Oncol 1994;12:26826.
6. Choy H, Rodriguez F, Koester S, et al. Synergistic effects of Taxol/Taxotere on radiation sensitivity on human tumor cell lines. J Radiat Oncol Biol Phys 1993;24:Suppl 1:1059.
7. Colevas D, Busse PM, Norris CM, et al. Induction Chemotherapy with docetaxel, cisplatin, fluorouracil, and leucovorin for squamous cell carcinoma of the head and neck: a Phase I/II trial. J Clin Oncol 1998;16: 1331–9.
8. Dimery IW, Hong WK. Overview of combined modality therapies for head and neck cancer. J Natl Cancer Inst 1993;85:95–111.
9. Dreyfuss AI, Clark JR, Norris CM, et al. Docetaxel: an active drug for squamous cell carcinoma of the head and neck. J Clin Oncol 1996;14:1672–8.
10. Fossella FV, Lee JS, Murphy WK, et al. Phase II study of docetaxel for recurrent or metastatic non-small-cell-lung cancer. J Clin Oncol 1994;12: 1238–44.
11. Fujii H, Sasaki Y, Ebihara S, et al. An early phase II study of docetaxel (Taxotere) in patients with head and neck cancer (ENG). Proc Am Soc Clin Oncol 1995;14:298.
12. Jackson SM, Weir LM, Hay JH, et al. A randomised trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997;43:39–46.
13. Jacobs C. Adjuvant and neoadjuvant treatment of head and neck cancers. Semin Oncol 1991;18:504–14.
14. Jerczek-Fossa B, De Braud F, Gasparetto M, et al. Induction chemotherapy followed by simultaneous hyperfractioned radiochemotherapy in advanced head and neck cancer. A pilot study. Strahlenther Onkol 1998; 174:457–61.
15. Geinitz H, Zimmermann FB, Molls M. Radiotherapy of the elderly patient. Radiotherapy tolerance and results in older patients. Strahlenther Onkol 1999;175:119–27.
16. Gupta NK, Pointon RCS, Wilkonson PM, et al. A randomized clinical trial to contract radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. Clin Radiol 1987;38:575.
17. Hainsworth JD, Burris HA, Erland JB, et al. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 1998;16:2164–8.
18. Hennequin C, Giocanti N, Favaudon V. Interaction of ionizing radiation with paclitaxel (Taxol) and docetaxel (Taxotere) in HeLa and SQ20B cells. Cancer Res 1996;15:1842–50.
19. Herscher LL, Hahn SM, Kroog G, et al. Phase I Study of Paclitaxel as a radiation sensitzer in the treatment of mesothelioma and non-small-cell lung cancer. J Clin Oncol 1998;16:635–41.
20. Hilkens PH, Verweij J, Vecht CJ, et al. Clinical characteristics of severe peripheral neuropathy induced by docetaxel (Taxotere). Ann Oncol 1997;8:187–90.
21. Hoffmann W, Belka C, Schmidberger H, et al. Radiotherapy and concomitant weekly 1-hour infusion of paclitaxel in the treatment of head and neck cancer- results from a phase I trial. Int J Radiat Oncol Biol Phys 1997;38:691–6.
22. Hoffmann W, Heinrich V, Belka W, et al. Präklinische und klinische Ergebnisse in der simultanen Radiochemotherapie von Kopf-Hals-Tumoren mit Paclitaxel. Strahlenther Onkol 1996;172:Suppl I:1–20.
23. Huguenin P, Glanzmann C, Taussky D, et al. Hyperfractionated radiotherapy and simultaneous cisplatin for Stage III and IV carcinomas of the head and neck. Long-term results including functional outcome. Strahlenther Onkol 1998;174:397–402.
24. Maurer AM, Masters GA, Haraf DJ, et al. Phase I study of Docetaxel with concomitant thoracic radiation therapy. J Clin Oncol 1998;16:159–64.
25. Merad M, Le Cesne A, Baldeyrou P, et al. Docetaxel and interstitial pulmonary injury. Ann Oncol 1997;8:191–4.

26. Merlano M, Corvo R, Margarino G, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. Cancer 1991;67:915–21.
27. Mirabell R, Allal AS, Mermillod B, et al. The influence of field size and other radiotherapy parameters on acute toxicity in pharyngolaryngeal cancers. Strahlenther Onkol 1999;175:74–7.
28. Mucke R, Blynow M, Ziegler PG, et al. Simultaneous radiochemotherapy with carboplatin in patients with inoperable advanced Stage III and IV head and neck tumors. Strahlenther Onkol 1999;175:213–17.
29. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. Br J Cancer 1995;71:83–91.
30. Posner M, Dryfuss A, Norris R, et al. A phase II trial of Docetaxel in squamous-cell carcinoma of the head and neck. Eur J Cancer 1995; 31A:Suppl 5:191.abstract 421.
31. Reckzeh B, Merte H, Pfluger KH, et al. Severe lymphopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. J Clin Oncol 1996;14:1071–6.
32. Tishler RB, Schiff PB Geard CR, et al. Taxol: a novel radiation sensitizer. Int J Radiat Oncol Biol Phys 1992;22:613–7.
33. van den Bent MJ, Hilkens PH, Sillevis Smitt PA, et al. Lhermitte's sign following chemotherapy with docetaxel. Neurology (NY) 1998;50: 563–4.
34. Varveris H, Delakas D, Anezinis P, et al. Concurrent platinum and docetaxel chemotherapy and external radical radiotherapy in patients with invasive transitional cell bladder carcinoma. A preliminary report of tolerance and local control. Anticancer Res 1997;17:4771–80.
35. Wendt TG, Grabenbauer GG, Rödel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 1998;16:1318–24.

Address for Correspondence: Priv.-Doz. Dr. Horst Jürgen Feldmann, Klinik für Strahlentherapie und Radiologische Onkologie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, D-81675 München, Phone (+49/89) 4140 - 4512, Fax -4587.