Preliminary Report

Reduced Incidence and Severity of Acute Radiation Mucositis by WF10 (IMMUNOKINE□) as Adjunct to Standard of Cure in the Management of Head & Neck Cancer Patients

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Objective: *To evaluate the role of WF10-immunotherapy in reducing oro-pharyngeal complications in head and neck cancer chemoradiotherapy.*
Material and Method: *Thirteen patients were enrolled and assigned either to WF10- (n = 6) or control group (n = 7). After completion of their initial (neoadjuvant) chemotherapy, patients received WF10 intravenous infusions at 0.5 mL/kg body weight/day for five consecutive days and repeated every 3 weeks, concomitantly to standard radiotherapy (6,600-7,500 cGy, 200 cGy/day). Control patients received radiotherapy alone.*
Results: *Patients in the WF10-group had a lower incidence of oro-pharyngeal complications grade > 2, including oral mucositis (1 vs. 5), dysphagia (2 vs. 7), oral pain (3 vs. 5), taste alteration (4 vs. 6) and weight loss (2 vs. 4). The statistical significances were achieved for the parameters of oral mucositis (p = 0.048) and dysphagia (p = 0.009).*
Conclusion: *WF10 appears to reduce severity of oro-pharyngeal complications associated with standard chemoradiotherapy for head and neck cancer.*

Keywords: *Tetrachlorodecaoxygen (TCDO iv, WF10), Chemotherapy, Radiotherapy, Mucositis, Head and Neck Cancer*

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Oro-pharyngeal complications are commonly encountered in standard therapy for head and neck cancer. Incidence and severity vary from patient to patient. Particular risk factors are age, nutritional status, type of malignancy and oral hygiene. The type of treatment applied also influences the outcome, particularly the number and the timing of chemotherapy cycles as well as the type of cytotoxic drug used. The various mucosal reactions include chemo- and radiotherapy-induced tissue damage, altered epithelial turnover, and inflammatory cell infiltration. Secondary complications arise with bacterial, fungal, and viral infections[1]. Most severe oro-pharyngeal complications are observed during concurrent chemo-radiotherapy. Virtually all patients with head and neck cancer who receive this treatment modality are affected[2]. The consequent delay or interruption of anticancer therapy may lead to treatment failure, shorten patient survival time and may result in increased therapeutic cost[3,4]. Oral mucositis, one type of oro-pharyngeal complication, is usually characterized by ulceration and pseudomembranes in the oral cavity. Internationally accepted scoring schemes assess radiation-induced oral mucositis by evaluating the general appearance (i.e. erythema), the extent of ulceration (i.e. pseudomembranes, discharge), and the patient's requirement for pain-controlling medication (i.e. analgesics, narcotics). Whereas, prevention of mucositis by prophylactic measures is generally considered less problematic, the treatment of already existing symptoms is much more challenging. Approaches with preventive intention include non-pharmacological ones, such as oral- or dental hygiene

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and pharmacological ones, for instance antibacterial, antifungal, antiviral agents and anti-inflammatory agents. Drugs, which specifically target potential pathogenetic mechanisms of mucositis, are being developed more recently, topically and systematically administered cytokines are among them. Granulocyte- (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) as well as transforming growth factor □3 (TGF-□3) appeared to be among the most promising ones[5,6]. WF10 (for intravenous infusion after dilution), is a chlorite-based drug which contains the active ingredient OXO-K993 (referred to as TCDO or tetrachlorodeca-oxygen in the literature). OXO-K993 is synthesized in a proprietary process by Dimethaid GmbH, Germany (formerly OXO Chemie GmbH). The pharmacologic activity of WF10 stems from its ability to modify the function of the monocyte-macrophage system, i.e. stimulation of phagocytosis and cellular defense systems[7-9]. The active principle of WF10, OXO-K993, has shown profound clinical benefit in patients with wound healing disorders[10]. Experiments in animal models suggested that WF10 treatment influences the time of onset, the grade of severity and the speed of healing of radiation-induced ulcers[11]. The results obtained in preclinical studies led to studies in cancer patients undergoing radiotherapy, using WF10 for treatment of late radiation cystitis[12,13].

Material and Method

Head and neck cancer patients with locally advanced disease, e.g. nasopharyngeal carcinoma (NPC) of stage III or IV (WHO type II or III), were targeted for the present study. All patients had previously received (neoadjuvant) chemotherapy with Cisplatin (100 mg/m^2 intravenously infused on Day 1) and 5-FU (1000 mg/m^2 intravenously infused over 24 hours on Days 1-3); one patient received Taxotere (70 mg/m^2 intravenously infused on Day 1), Carboplatin (300 mg/m2 intravenously infused on Day 1) and 5-FU (1000 mg/m^2 intravenously infused over 24 hours on Days 1-3). Other eligibility criteria were age between 18 and 75 years, Karnofsky performance score $\geq$ 60, white blood cell count > 2,500/mm^3, platelet count > 80,000/mm^3, hemoglobin > 10.0 g/dL and, no significant renal or hepatic impairment.

Patient Selection

Patients were identified at the outpatient department (OPD) and selected in pairs of comparable patients with similar characteristics. After eligibility was confirmed, the investigator randomly assigned one patient to the WF10-group and the other one to the control group. It was the intention to generate two study groups, for the study's eligibility criteria, history, and stage of disease, treatment history, age, sex, weight, oral hygiene, and nutritional status.

Treatment

External beam radiation was delivered using ^{60}Cobalt-teletherapy (Theratron 780C) with daily fraction sizes of 200 cGy per day and 5 days per week to the primary site and regional lymph nodes. The tumor and upper cervical lymph nodes were treated with two parallel, laterally opposed fields. The median lower parts of the neck and supraclavicular lymph nodes were treated using a single anterior field with midline blocking. Spinal cord protection was introduced after 48 Gy. The total dose delivered to the primary tumor and involved lymph nodes was 66-75 Gy (The upper cervical node received an additional 9 Gy from posterior field).

Following neoadjuvant chemotherapy, radiotherapy was given over a period of 6-8 weeks. Day 1 of radiotherapy was also the first day of WF10 treatment. Each patient, assigned to the WF10 group, received standard radiotherapy plus WF10 therapy at 0.5 mL/kg body weight per day, diluted in 500 mL 5% dextrose water (5% D/W), administered by intravenous infusion over a period of 4 hours for 5 consecutive days, after radiation fractions and repeat the treatment every 3 weeks for 3 cycles, i.e. treatment cycles were administered from Days 1 to 5 in Weeks 1, 4 and 7. The patients in the control group received standard radiotherapy alone. Further concomitant medication was administered according to symptoms including analgesics, ferrous sulfate (iron supplement) and blood transfusions with packed red blood cells.

The present study evaluated the effects of WF10 on incidence and severity of treatment-induced oro-pharyngeal complications using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 and the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria for mucous membranes. Examination of the oral cavity was performed twice weekly and the results were documented in appropriate case report forms (CRFs). Efficacy parameters in the present study included oral mucositis, oral pain, dysphagia, taste alteration, and weight loss. Interruptions or discontinuations of the standard radiotherapy schedule, if necessary, were also recorded and evaluated. Safety was assessed throughout the present study by evaluation of complete blood cell count (CBC), blood chemistry (BUN, creatinine, SGOT/SGPT and

bilirubin), and physical examination according to the WHO toxicity grading criteria (recommended for acute and sub-acute toxic effects).

The efficacy endpoints of the present study were the development of any oro-pharyngeal complication with a severity grade ≥ 2 in any of the efficacy parameters and interruption or discontinuation of the standard radiotherapy schedule due to the patients' intolerance to continue the treatment.

Statistical analysis

For comparison of continuous variables, a Mann Whitney U-test (two-tailed) was used, whereas categorical variables were compared using Fishers' Exact test.

Results

From May 2004 to May 2005, thirteen patients with histologically proven head and neck cancers entered the present study. Of the eligible patients, six were selected to the WF10-group and seven as the control group. The patients' clinical characteristics are listed in Table 1. Among the 13 patients, 10 had carcinoma of the nasopharynx (NPC), four in the WF10-group and six in the control group. Each group included one patient with an unknown primary tumor. One patient enrolled in the WF10-group had a tumor of the buccal mucosa. There was no statistical difference between the groups with respect to tumor site, tumor stage, and histopathology. All patients were included in the final analysis.

Chemotherapy and radiotherapy

All (n = 13) patients were planned to receive 6 courses of chemotherapy as (3 courses of neo-adjuvant, then radiotherapy and another 3 courses of adjuvant chemotherapy) Of these, 12 patients had received neo-adjuvant of Cisplatin (100 mg/m^2 intravenously

Table 1. Patient characteristics

Characteristics	WF10		Control	
	No. of patients	%	No. of patients	%
Total Patient Number	6		7	
Age at randomization, years				
Median	54.5		48.0	
Mean $\pm$ SD	55.5 $\pm$ 9.5		51.4 $\pm$ 9.9	
Range	42-71		38-62	
Sex				
Male	6	100	5	71
Female	-	0	2	29
Body weight				
Median	57.1		59.0	
Mean $\pm$ SD	56.5 $\pm$ 5.8		55.4 $\pm$ 14.6	
Range	46.5-63		30.0-71.5	
Karnofsky Performance Status				
Range	80		70-80	
Cancer Site				
Nasopharynx	4	67	6	86
Buccal mucosa	1	17	0	0
Unknown	1	17	1	14
Stage				
IIB	0	0	1	14
III	1	17	2	29
IV	1	17	1	14
IVA	1	17	1	14
IVB	3	50	2	29
Histopathology				
Moderate diff squamous cell	1	17	0	0
Poorly diff squamous cell	2	33	5	71
Undifferentiated	3	50	2	29

on Day 1) and 5-Fluorouracil (1000 mg/m^2 intravenously infused over 24 hours on Days 1-3) and 1 patient had received another regimen; Taxotere (70 mg/m^2 Day 1), Carboplatin (300 mg/m^2 Day 1) and 5-FU (1000 mg/m^2 intravenously infused over 24 hours on Days 1-3). After completion of radiotherapy, additional courses of adjuvant chemotherapy were planned. Details of standard treatment are summarized in Table 2.

With an increasing number of radiation fractions (2 Gy/day x 5/week), patients were at higher risk of developing oro-pharyngeal complications. Typically, complications developed after Week 3 ($\geq$ 30 Gy) with severities of grade $\geq$ 2, requiring intervention, e.g. pain reducing medications or interruption of treatment.

Distribution of grading

Assessment and grading were performed twice weekly, on Day 1 and Day 5. The results of a comparison between the present study groups with respect to objective and subjective parameters, evaluated in the present study, are summarized and illustrated in Fig. 1 to 5. A summary of the proportion of patients who suffered from grade $\geq$2 oro-pharyngeal complication is presented in Table 3.

Oral mucositis

Patients in both groups remained free of significant oral mucositis during the first 4 weeks of radiotherapy. Whereas, mild oral mucositis developed from

Table 2. Neoadjuvant chemotherapy and radiation therapy

	WF10		Control	
	No. of patients	%	No. of patients	%
Total Patient Number	6		7	
Chemotherapy				
Cisplatin + 5FU	5	83	7	100
Taxotere + Carboplatin + 5FU	1	17	0	0
Dose to primary tumor (Gy)				
Median	72		72	
Range	66-72		54-72	
Dose to node (Gy)				
Median	75		75	
Range	66-75		54-75	
Number of patients need RT interruption	0	0	3	43
Number of patients received 6 course of chemotherapy	3	50	2	29
Time from day 1 to xylocain treatment				
Mean $\pm$ SD	21.2 $\pm$ 10.7		16.4 $\pm$ 9.8	
Number of patients need blood transfusion	6	100	4	57

Table 3. Proportions of patients suffering from grade $\geq$ 2 in parameters of oral complication

Parameter*	WF10		Control	
	No. of patients	%	No. of patients	%
Total N	6	100	7	100
Oral Mucositis	1	17	5	71
Oral Pain	3	50	5	71
Dysphagia	2	33	7	100
Taste Alteration	4	67	6	86
Weight Loss	2	33	4	57

*All patients who had developed grading $\geq$ 2 at any point during radiotherapy have been included into this summary table

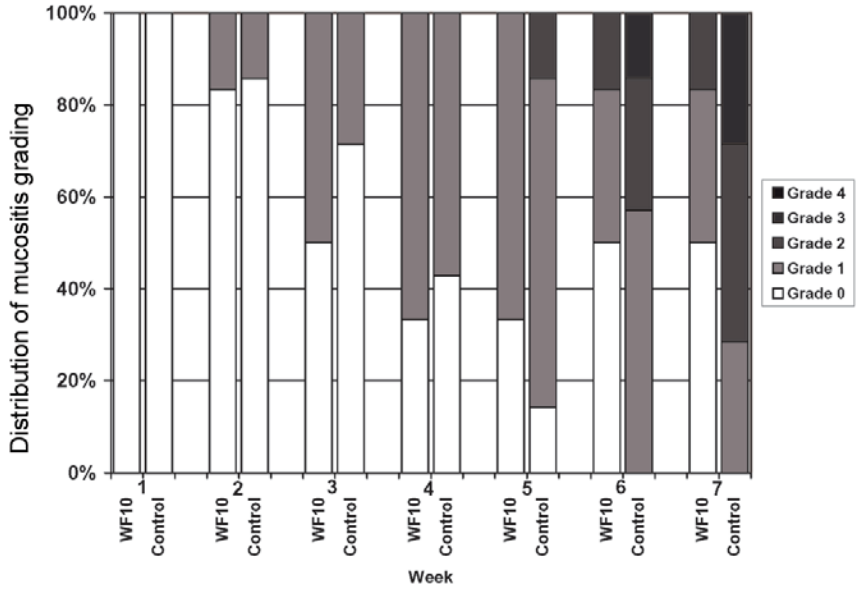

Fig. 1 Distribution of mucositis during radiation therapy (7 weeks), comparison between control group and WF10 group

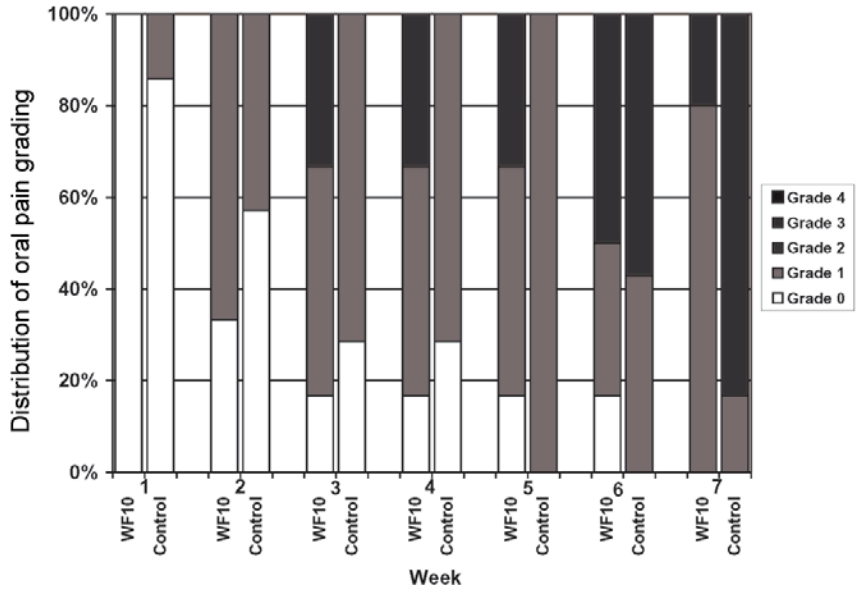

Fig. 2 Distribution of oral pain during radiation therapy (7 weeks), comparison between control group and WF10 group

Week 2 on, grade 2 oral mucositis developed in Week 5, it applied only to the control group. At Week 7, 3 control patients had developed grade 2, and 2 patients had developed grade 3 oral mucositis, whereas, in the WF10 group 5 patients displayed grade 0-1 and only 1 patient displayed grade 2 oral mucositis. There were significantly fewer patients with oral mucositis grade ≥ 2 in the WF10 group (p-value = 0.048).

Oral pain

Patients in both study groups did not report any significant oral pain until Week 3. At Week 7, 5 of

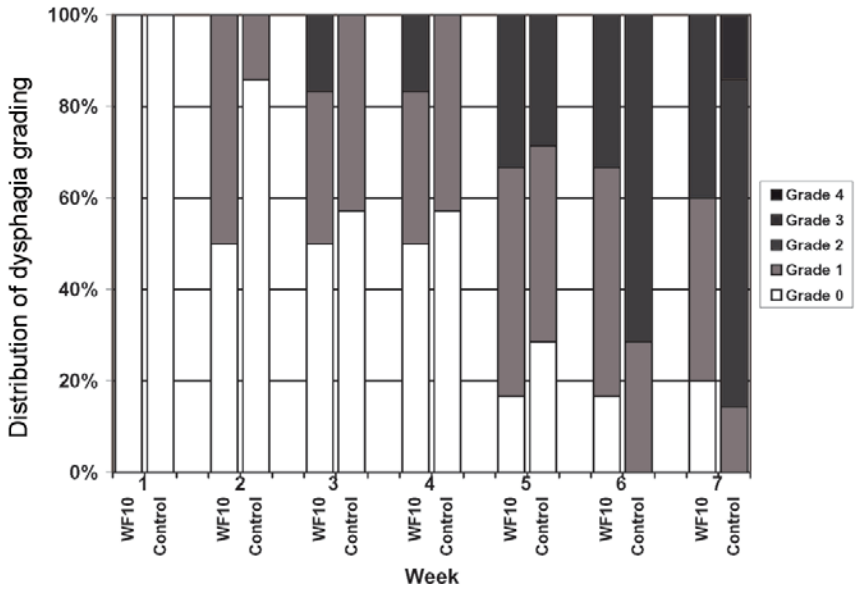

Fig. 3 Distribution of dysphagia during radiation therapy (7 weeks), comparison between control group and WF10 group

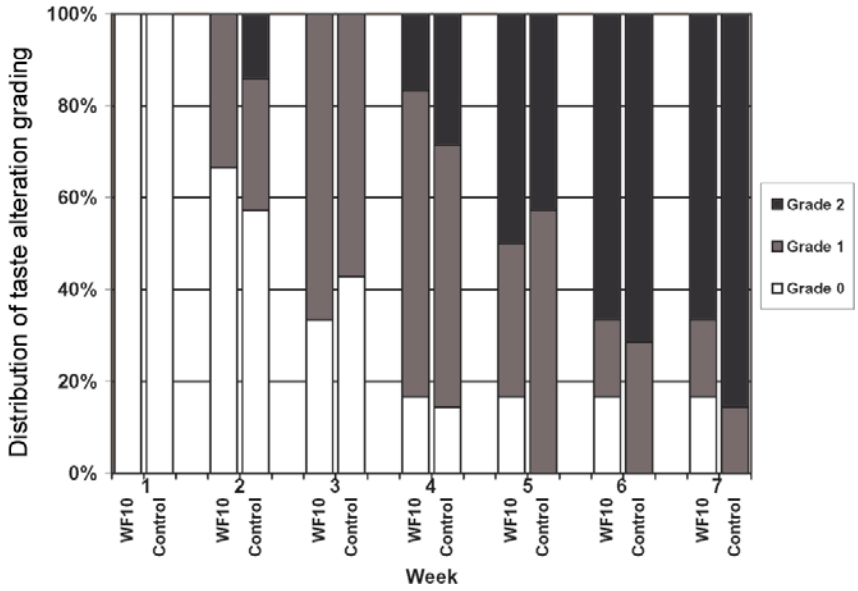

Fig. 4 Distribution of taste alteration during radiation therapy (7 weeks), comparison between control group and WF10 group

6 patients in the control group reported grade 2 oral pain versus 1 of 5 patients in the WF10 group. However, one patient in the WF10 group, who had reported grade 2 oral pain since Week 3, had a missing value in Week 7 due to complete radiotherapy and discharged. The difference in oral pain grade ≥ 2, between WF10- and control group, was not statistically significant (p-value = 0.429).

Dysphagia

Dysphagia was reported by the patients as early as Week 2, however, only to a mild degree until Week 3

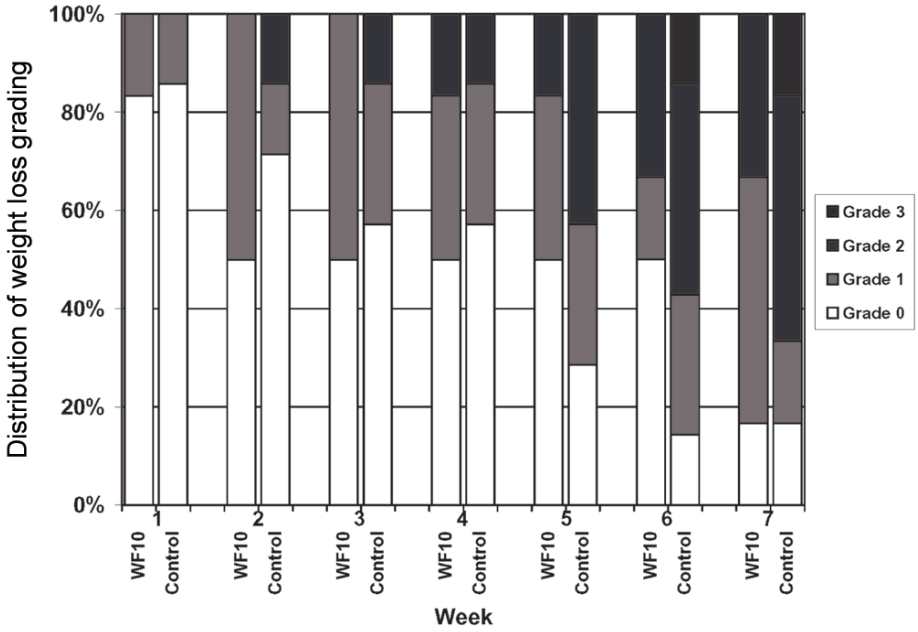

Fig. 5 Distribution of weight loss during radiation therapy (7 weeks), comparison between control group and WF10 group

and 4. From Week 5 on, patients in both groups displayed grade 2 dysphagia. Until Week 7, the number of patients with dysphagia grade ≥ 2 remained stable at 2 in the WF10 group, but increased in the control group from 2 in Week 5, to 5 in Week 6 and to 6 in Week 7. The difference in the number of patients with grade ≥ 2 dysphagia, between WF10- and control group, was statistically significant (p-value = 0.009).

Taste alteration

In the control group, one patient developed taste alteration grade 2 at Week 2. The first patient to develop grade 2 in the WF10 group emerged in Week 4. At Week 7, 6 of 7 patients in the control group were affected by taste alteration (grade 2) compared to 4 of 6 in the WF10 group. This difference was not statistically significant (p-value = 0.416).

Weight loss

Grade 2 weight loss appeared first in the control group in Week 2 (1/6). At Week 5, the number of patients with grade ≥ 2 weight loss rose to 4. In the WF10 group, 1 patient developed grade 2 weight loss in Week 4 and another one in Week 6. No grade 3 weight loss was observed in the WF10 group, whereas one patient (1/7) in the control group developed grade 3 in Week 6. A comparison graph of mean percent of body weight loss in both groups is presented in Fig. 6.

Interruptions

Three of seven (3/7 = 43%) control patients had to interrupt their radiotherapy schedule, whereas none of the WF10 treated patients required an interruption. The first patient interrupted for one week after 29 fractions, the second patient interrupted for 4 weeks due to severe dysphagia after 29 fractions. The third patient interrupted after 28 fractions and refused further therapy due to her poor general condition. She could not recover from radiation-induced toxicities and expired three weeks later.

Safety

Low hemoglobin levels and anemia are common in cancer patients under chemo- and radiotherapy, especially in the rural Northeastern part of Thailand. The present study was no exception. The group of WF10 treated patients already began radiotherapy (after neoadjuvant chemotherapy) with a mean hemoglobin value of only 10.4 g%, which already represents grade 1 toxicity (WHO). This level dropped continuously (except 10.1 g% at Week 3) to 9.3 g% at Week 6, which represents a grade 2 toxicity. Individual patients in the WF10 group also developed grade 3 and grade 4 toxicities. The control group began radiotherapy at a mean hemoglobin level of 11.1 g%, which dropped to 10.2 g% at Week 6. Individual patients in the control group developed grade 2 hemoglobinemia during the present

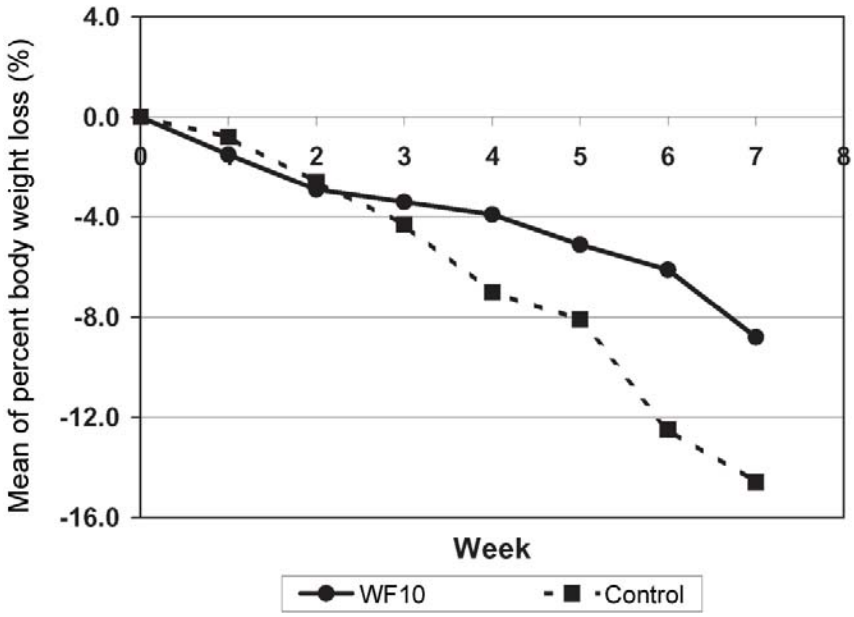

Fig. 6 Mean percent loss of body weight over the 7-week period of radiation therapy, comparison between control group (RT alone) and WF10 group (RT plus WF10)

study. Blood transfusions were administered when a patient displayed hemoglobin values below 10.0g%. All WF10 treated patients required blood transfusions (6 of 6 patients, a total of 24 units), compared to only 4 patients (4 of 7 patients, a total of 8 units) in the control group, which may be in line with WF10's mode of action. More patients in the WF10 group (n = 4) versus patients in the control group (n = 2) developed severe (grade $\geq$ 2) leucopenia. Apart from hematological changes, WF10 therapy, in this setting, appears to be well tolerated. One patient of the control group discontinued treatment in Week 6 and died during treatment interruption in Week 9. Her death was due to severe side effects of chemo- and radiotherapy and her poor general condition. Apart from hemoglobinemia and leucopenia, all other laboratory parameters remained stable and in normal range in both groups (Table 4).

Discussion

Thirteen adult head and neck cancer patients were enrolled into this single center, two-arm, open-label study. Included were patients who had completed their initial (neoadjuvant) chemotherapy and were, when the present study began, entering standard radiotherapy (6,600-7,500 cGy) with daily fractions of 200 cGy. Patients were assigned to their treatment groups at the discretion of the investigator with an attempt to achieve equal distribution of patient demographics

Table 4. Treatment toxicities during treatment*

WF10 Group (n = 6)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobinemia			n = 5		n = 1
Leukopenia		n = 2	n = 4		
Control Group (n = 7)	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobinemia	n = 1	n = 3	n = 3		
Leukopenia	n = 1	n = 4	n = 2		

*renal, hepatic and other hematological remained all in normal range and are not shown

and all major clinical variables in both groups. Patients assigned to the WF10 group received 3 cycles of WF10 therapy at a dose of 0.5 mL per kg body weight, concomitant to radiotherapy. Patients in the WF10-group received WF10-infusions for 5 consecutive days in Weeks 1, 4 and 7. The objective of the present study was to evaluate the effect of WF10 on oro-pharyngeal complications during radiotherapy, assessed by questioning and physical examination, using internationally accepted scoring systems.

Acute oro-pharyngeal complications are serious side effects of radiation therapy. However, even severe grades of oral mucositis are usually temporary and may be considered acceptable by the patient and the treating doctor in the view of the ultimate treatment goal, which is the elimination of the cancer. Thus, interruptions or discontinuations of radiotherapy, due to radiation-induced toxicities or to general intolerance to the treatment, were also recorded. Treatment interruptions or discontinuation of standard treatment put the patient at a significant risk of treatment failure, cancer recurrence, and death. Thus, avoidance of interruptions, due to any intolerance of standard treatment, should be considered the essential reason for adjuvant immunotherapy with an adjunct such as WF10. The rationale for WF10 in the indication studied here derives from its dual mode of action, which provides natural anti-inflammation as well as enhanced innate immune response targeting secondary infection and tumor killing[14-21]. The safety profile of WF10 was to be evaluated by monitoring relevant hematological and other laboratory parameters. The results show that patients treated with WF10 had a lower incidence of oro-pharyngeal complications of grade ≥ 2 in all parameters measured, whereas a higher number of patients with serious radiation-induced oro-pharyngeal complications were found in the control group. The corresponding weight loss was also less pronounced in the WF10 group. The difference between the study groups reached statistical significance in the parameters oral mucositis and dysphagia. Oro-pharyngeal complications and other clinical conditions, such as weakness and fatigue led to treatment interruptions in three patients of the control group, whereas no treatment interruptions became necessary in the WF10 group. Potential advantage, derived from this fact, may be a prolonged disease free- and overall survival, which would be the subject of a follow up and possibly to be investigated in a larger study. With respect to safety, analysis of laboratory parameters provided no evidence of any clinically relevant toxicity to the hematopoietic-, digestive- or any other body system. The decrease of blood hemoglobin levels in some patients was generally expected and consistent with the patients' condition at this stage of disease and under this specific therapy regime. The drop of hemoglobin levels in some WF10 treated patients may be derived from WF10's mode of action, which entails augmented phagocytic activity of senescent or damaged red blood cells. The striking advantage in treatment interruptions and the statistically significant difference in the number of patients who developed grade ≥ 2 oral mucositis and dysphagia, and the obvious trends in the other parameters of oral complications, indicate the clinical efficacy of WF10 in the reduction of oro-pharyngeal complications during radiotherapy in the management of head and neck cancer patients. Although the low number of patients enrolled into this pilot study precludes a definite interpretation, the results suggest a role of WF10 as an adjunct in the treatment of cancer. The conduct of further studies is warranted to optimize treatment schedules, possibly in combination with other modalities (i.e. concurrent chemo-radiotherapy), for improved outcome and prolonged survival.

Conclusion

WF10 appears to provide therapeutic benefit in the reduction of oral complications; mucositis and dysphagia associated with standard radiotherapy for head and neck cancer. The potential to reduce the severity of other oro-pharyngeal complications, as observed in the present study, should be investigated in larger, randomized studies.

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การประเมินประสิทธิภาพของ IMMUNOKINE® (WF10) ในการป้องกันการเกิดเยื่อบุช่องปากอักเสบจากการฉายรังสีรักษามะเร็งบริเวณศีรษะและคอ

สมคิด เพ็ญพัธนกุล

วัตถุประสงค์: *การศึกษานำร่องนี้เพื่อประเมินบทบาทของยา WF10 ในการลดอาการแทรกซ้อนในช่องปากและคอจากการใช้เคมีบำบัดเพื่อรักษามะเร็งบริเวณศีรษะและคอ*

วัสดุและวิธีการ: *ผู้ป่วย 13 รายถูกแบ่งเป็นกลุ่มที่ได้รับ WF10 (n = 6) และกลุ่มเปรียบเทียบ (n = 7) ภายหลังเสร็จสิ้นเคมีบำบัด ผู้ป่วยจะได้รับ 0.5 mL/kg WF10 โดยหยดเข้าลหอดเลือดดำ 5 วันติดต่อกันทุก 3 สัปดาห์พร้อมกับการฉายรังสีมาตรฐาน (6,600-7,500 cGy, 200 cGy/day) ส่วนกลุ่มเปรียบเทียบจะได้รับการฉายรังสีอย่างเดียว*

ผลการศึกษา: *พบว่า ผู้ป่วยกลุ่ม WF10 มีอาการแทรกซ้อนในช่องปากและคอระดับ $\geq$ 2 น้อยกว่า ได้แก่ เยื่อบุช่องปากอักเสบ (1:5, p = 0.048) กลืนลำบาก (2:7, p = 0.009) เจ็บในปาก (3:5, p = 0.429) การรับรสเปลี่ยน (4:6, p = 0.416) และน้ำหนักลด (2:4, p = 0.391)*

สรุป: *ยา WF10 สามารถลดความรุนแรงของอาการแทรกซ้อนดังกล่าว ที่เกิดจากการรักษามะเร็งบริเวณศีรษะและคอตามมาตรฐานได้อย่างมีนัยสำคัญ*