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ORIGINAL ARTICLE

Compliance and toxicity of the hypoxic radiosensitizer nimorazole in the treatment of patients with head and neck squamous cell carcinoma (HNSCC)

MOHAMED A. HASSAN METWALLY[1], KATRINE DIEMER FREDERIKSEN[2] & JENS OVERGAARD[1]

[1]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark and* [2]*Department of Oncology, Odense University Hospital, Odense, Denmark*

ABSTRACT

Purpose. To evaluate the compliance and toxicity of the hypoxic radiosensitizer nimorazole in head and neck cancer patients.
Methods. A retrospective study of patients with head and neck squamous cell carcinoma (HNSCC), treated in Denmark between 1990 and 2013. All patients treated with radical radiotherapy (± chemotherapy) [66–70 Gy; 33–35 fractions; 2 Gy/fraction; 5–6 fractions/week] concomitant with the hypoxic radiosensitizer nimorazole. Nimorazole was administered as oral tablets in doses of approximately 1.2 g/m^2 body surface area in connection with the first of each daily radiation treatment. A second daily dose of 1 g was given in connection with the second radiotherapy fraction in the accelerated fractionation regimen. The compliance was estimated as the percentage of the initially prescribed dose, which was received by each patient. The main side effects were recorded.
Results. A total of 1049 patients were investigated. The tolerance to nimorazole was fair: 58% of patients received the full prescribed total dose. Nausea and vomiting were the major complaints: among the 260 patients with dose reductions due to known side effects, (87%) were due to nausea/vomiting. All side effects ceased when treatment was interrupted, and neither severe nor long lasting side effects were observed. Female patients were significantly more likely to have dose reduction (OR 2.02; 95% CI 1.50–2.70), and nausea/vomiting. Patients aged more than 70 years were significantly more likely to have dose reduction. Patients who received less than 1100 mg/m^2 were significantly less likely to have dose reduction (OR 0.58; CI 0.44–0.78), and nausea/vomiting, compared to those who received 1100–1300 mg/m^2. The tolerance was also less in the group of patients received accelerated chemoradiotherapy (OR 1.70; CI 1.20–2.50) with more association with nausea/vomiting (OR 2.09; CI 1.40–3.10).
Conclusion. The compliance to nimorazole is fair, with tolerable acute, but neither persistent nor late, toxicity. It can be administered with chemotherapy and different radiotherapy fractionation schedules.

Hypoxia plays a major role in the tumor response to radiation in patients with head and neck cancer [1,2]. It has been demonstrated in major randomized clinical trials and meta-analyses [1,3] that modification of hypoxia during radiotherapy results in significant better loco-regional tumor control, disease specific and overall survival.

The use of the 2-nitro-imidazole hypoxic radiosensitizer misonidazole [3,4] improved the response to irradiation, but neurotoxicity in the form of delayed peripheral neuropathy severely restricted the total dose which could be given in the course of radiotherapy [3,5–8]. The 5-nitro-imidazole nimorazole, however, demonstrated significant improved tumor control after irradiation in patients with squamous cell carcinoma of the head and neck (HNSCC) with neither serious nor long-lasting side effects, and especially without neurotoxicity [9,10]. Thus, nimorazole was introduced as a routine treatment in 1990 to all Danish patients treated with curative radiotherapy for HNSCC (except patients with small glottis tumors).

Correspondence: M. A. Hassan Metwally, Department of Experimental Clinical Oncology, Aarhus University Hospital, Nørrebrogade 44, bld. 5, 8000 Aarhus C, Denmark. Tel: + 45 50 311647. E-mail: hassan@oncology.dk

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A poor compliance introduces a major risk of bias in the interpretation of the results of the therapeutic clinical trials. It affects the course of many diseases, even those with a fatal prognosis [11]. As poor compliance can undermine the execution and validity of clinical trials, it represents an essential parameter in the analysis of the outcome [12].

The aim of the present study was therefore to evaluate the vast Danish experience regarding the compliance and toxicity of nimorazole drug treatment in head and neck cancer patients, when treatment with radiotherapy given either alone with conventional or accelerated fractionation [13,14] or in combination with accelerated chemo-radiotherapy with weekly cisplatin [14–16], since such treatment schedules are widely used, and furthermore all are part of ongoing or planned large clinical trials.

Patients and methods

We analyzed, in a retrospective study, patients with HNSCC treated in two oncological centers in Denmark between 1990 and 2013. All accessible patients treated with radical radiotherapy concomitant with the hypoxic radiosensitizer nimorazole, who completed a full radiotherapy course (at least 30 fractions) according to the various Danish Head and Neck Cancer Group (DAHANCA) protocols and guidelines [17], were included. The data were collected from the DAHANCA database, and missing information was completed through review of the patient charts. All patients received radical intended radiotherapy (with or without concomitant chemotherapy) to a total dose of 66–70 Gy given in 33–35 fractions with 2 Gy per fraction. Radiotherapy was given initially as conventional fractionation (5 fractions/week), but later as a consequence of the DAHANCA 7 trial [18] did patients receive accelerated fractionation (6 fractions/week). Concomitant chemotherapy was given with weekly cisplatin with a dose of 40 mg/m^2 body surface area (BSA).

Nimorazole was administered as orally (500 mg tablets) in doses of approximately 1.2 g/m^2 BSA in connection with the first of each daily radiation treatment [19,20]. The prescribed number of tablets was either three (1500 mg for patients with <1.6 m^2 BSA), four (2000 mg for patients with 1.6–1.9 m^2 BSA), or five (2500 mg for patients with >1.9 m^2 BSA) tablets. A second daily dose of 1 g (two tablets) was given in connection with the second radiotherapy fraction (once per week) in the accelerated fractionation regimen. The drug was given 90 minutes prior to the radiation treatment.

The full compliance to the drug treatment was defined as: receiving a total dose (in mg) equivalent to the total dose of the planned successive 30 drug fractions, according to the prescribed daily dose and the radiotherapy fractionation schedule. Thus, the compliance was estimated as the percentage of the initially prescribed dose, that was received by each patient, and the number of radiotherapy fractions given together with nimorazole.

The patients were analyzed according to the following three treatment groups: accelerated chemo-radiotherapy; accelerated radiotherapy alone or conventional fractionated radiotherapy alone. The main side effects of nimorazole (nausea/vomiting, flushing, and skin rash) were recorded. Nausea/vomiting was scored according to the severity of the symptom into three scores (1: mild; 2: moderate; 3: severe causing disruption of treatment).

Statistical analysis

Frequency tables with counts and percentages were used to describe the cohort of patients and their distribution in the different treatment groups. Univariate and multivariate logistic regression models were used

Table I. Distribution of patients' characteristics and treatment-related variables.

Covariates	Male	Female	Total
Age			
Range	17–87	29–90	17–90
Median	59	62	60
≤40 years	17 (2%)	2 (1%)	19 (2%)
41–50 years	114 (15%)	37 (14%)	151 (14%)
51–60 years	290 (37%)	82 (31%)	372 (35%)
61–70 years	257 (33%)	98 (36%)	355 (34%)
>70 years	104 (13%)	48 (18%)	152 (15%)
Performance WHO*			
0–1	694 (93%)	236 (93%)	930 (93%)
2–3	50 (7%)	19 (7%)	69 (7%)
Tumor site			
Larynx	229 (29%)	72 (27%)	301 (29%)
Pharynx	468 (60%)	154 (58%)	622 (59%)
Oral cavity	85 (11%)	41 (15%)	126 (12%)
Stage			
I–II	363 (46%)	149 (56%)	512 (49%)
III–IV	419 (54%)	118 (44%)	537 (51%)
Chemotherapy			
No CT	629 (80%)	233 (87%)	862 (82%)
With CT	153 (20%)	34 (13%)	187 (18%)
Fx/week			
5	139 (18%)	70 (26%)	209 (20%)
6	643 (82%)	197 (74%)	840 (80%)
Given dose			
1500 mg	31 (4%)	95 (36%)	126 (12%)
2000 mg	344 (44%)	151 (56%)	495 (47%)
2500 mg	407 (52%)	21 (8%)	428 (41%)
Dose/m²§			
<1100 mg/d	220 (28%)	122 (47%)	342 (33%)
1100–1300 mg/d	523 (68%)	135 (51%)	658 (64%)
>1300 mg/d	31 (4%)	5 (2%)	36 (3%)

*missed data in 50 patients; §missed data in 13 patients.

to identify association of the patient characteristics and the treatment-related factors with the received total dose and the incidence and severity of side effects. A stepwise selection procedure was used to build the multivariate logistic regression model. Entry criterion was set at $p<0.10$. The odds ratios for each variable in the final model along with their 95% confidence intervals (CIs) and p-values were reported. The odds ratios estimate how much more (less) likely it is to be in the case group versus the control group among patients with the specific variable group's characteristic.

Results

A total of 1049 patients were investigated. The patient and tumor characteristics are given in Table I. The tolerance to nimorazole was fair and overall 613 patients (58%) received the full prescribed total dose of the drug. Table II shows the distribution of patients according to radiotherapy treatment groups and drug compliance. All side effects ceased when treatment was interrupted, and neither severe nor long-lasting side effects were observed. Many patients completed the sensitizer treatment without any notable symptoms, whereas nausea and vomiting were the major complaints in the remaining group. In addition, a few other symptoms were described, mainly in the form of flushing and skin rash. Table II shows that, of the 436 patients who did not receive the full dose, 342 patients had a dose reduction due to a known recorded cause. This was in 319 patients (93%) due to side effects, whereas 23 patients (7%) had a reduction due to other causes (11 patients: due to difficulty in swallowing of the tablets; five patients: due to logistic reasons; one patient: due to sensory neuropathy; one patient: due to depressive feeling for hours after treatment; one patient: due to chest tightness after the drug intake; four patients: due to the doctor decision).

Among the 260 patients with dose reductions due to known side effects (Table II) (87%) were due to nausea and vomiting, (3%) were due to flushing, and were due to skin rash. The distribution of compliance and the cause of dose reduction and the type of side effects were unrelated to the different

Table II. Distribution of patients on the treatment groups as a function of compliance and side effects.

		All patients (1049)								
		No CT 862 (82%)						With CT 187 (18%)		
		5 fx/wk 209 (62%)			6 fx/wk 653 (62%)			6 fx/wk 187 (18%)		
		1.5 g/d	2 g/d	2.5 g/d	1.5 g/d	2 g/d	2.5 g/d	1.5 g/d	2 g/d	2.5 g/d
		37	117	55	77	313	263	12	65	110
Sex										
Male	782 (74.5%)	9	77	53	19	222	249	3	45	105
Female	267 (25.5%)	28	40	2	58	91	14	9	20	5
Compliance										
Fully compliant	613 (58.4%)	25	64	34	49	199	150	1	35	56
Non-compliant	436 (41.6%)	12	53	21	28	114	113	11	30	54
Reported side effects (with & without dose reduction) (419)*										
N&V 1	96	4	18	5	7	31	20	2	2	7
2	113	4	24	13	10	26	25	1	5	5
3	210	8	23	7	15	53	44	6	15	39
Flushing	27	1	10	3	1	11	1	0	0	0
Skin rash	41	2	12	3	3	12	6	0	1	2
Causes of total dose reduction (436)										
Side effects	319	11	39	13	24	81	79	8	19	45
Other causes	23	0	2	1	0	5	8	1	3	3
Unknown	94	1	12	7	4	28	26	2	8	6
Side effects as a cause of dose reduction (319)										
N&V	227	10	28	8	18	52	49	8	15	39
Flushing	6	0	1	2	1	1	1	0	0	0
Skin rash	27	1	8	1	2	8	5	0	1	1
Unknown	59	0	2	2	3	20	24	0	3	5

CT, chemotherapy; fx/wk, fractions/week; N&V, Nausea and Vomiting; N&V 1 2 3, Nausea and vomiting grade 1 or 2 or 3.
*including the concurrent incidence of side effects in the same patient.

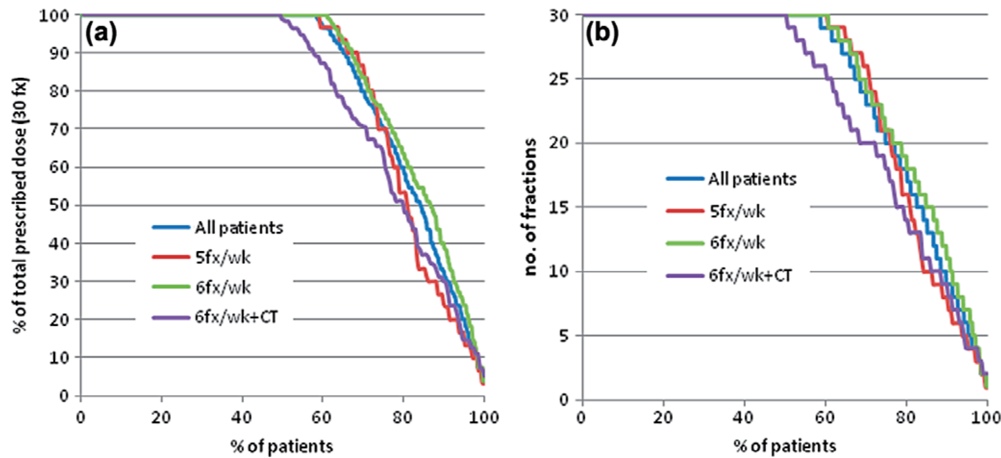

Figure 1. The relation between the drug received and the percentage of patients. (a) Drug received expressed as a percentage of the prescribed dose. (b) Drug received expressed as the number of the drug fractions. CT, chemotherapy; fx, fractions.

radiotherapy treatment groups. This is further illustrated in Figure 1 which shows the compliance to nimorazole treatment expressed as either number of given drug fractions or percentage of planned total drug dose as a function of treatment group. Figure 1 also illustrates that the group of patients who received accelerated chemo-radiotherapy was slightly less compliant to nimorazole than the other two groups given radiotherapy alone. Females were generally less compliant to the drug treatment, regardless of the treatment group (Figure 2) whereas their given daily dose (1500 vs. 2000 vs. 2500 mg/day) did not influence the compliance (Figure 3).

A logistic regression analysis of the pretreatment and the treatment-related variables is presented in Table III. When using dose reduction of nimorazole

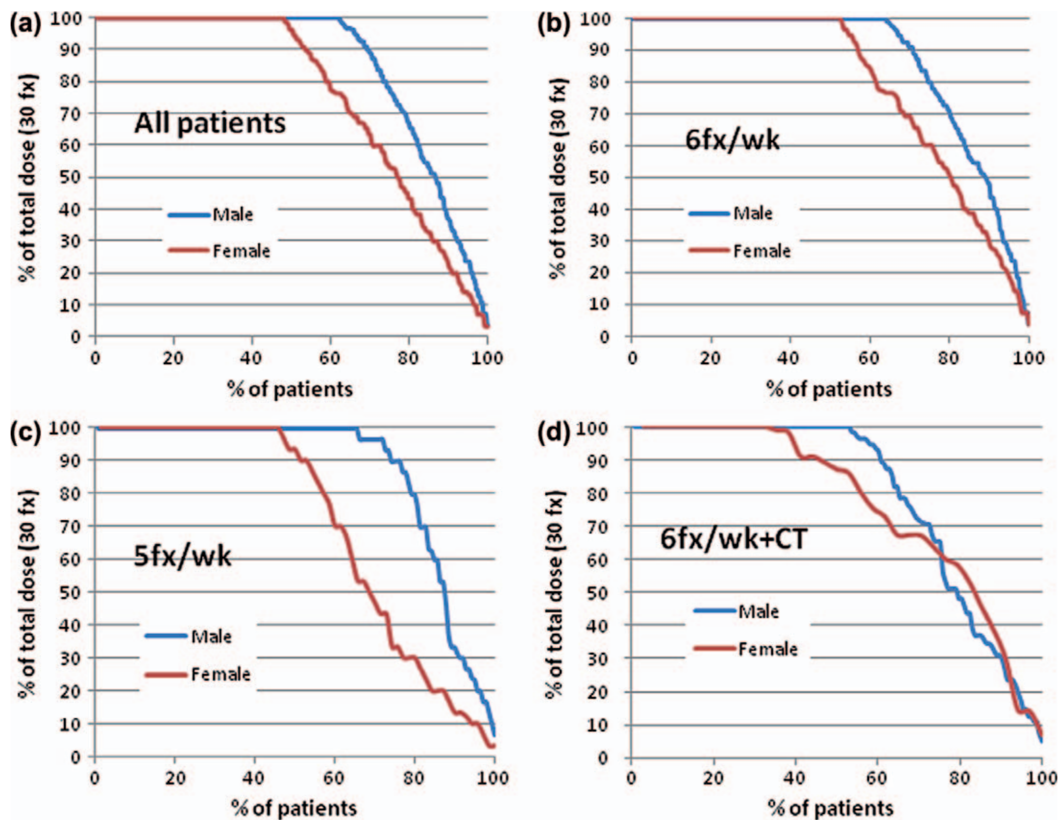

Figure 2. The relation between the percentage of patients and the percentage received of the full prescribed dose (as a function of sex). (a) In all patients. (b) In the accelerated fractionation treatment group. (c) In the conventional fractionation treatment group. (d) In the accelerated fractionation + chemotherapy treatment group. CT, chemotherapy; fx, fractions; wk, week.

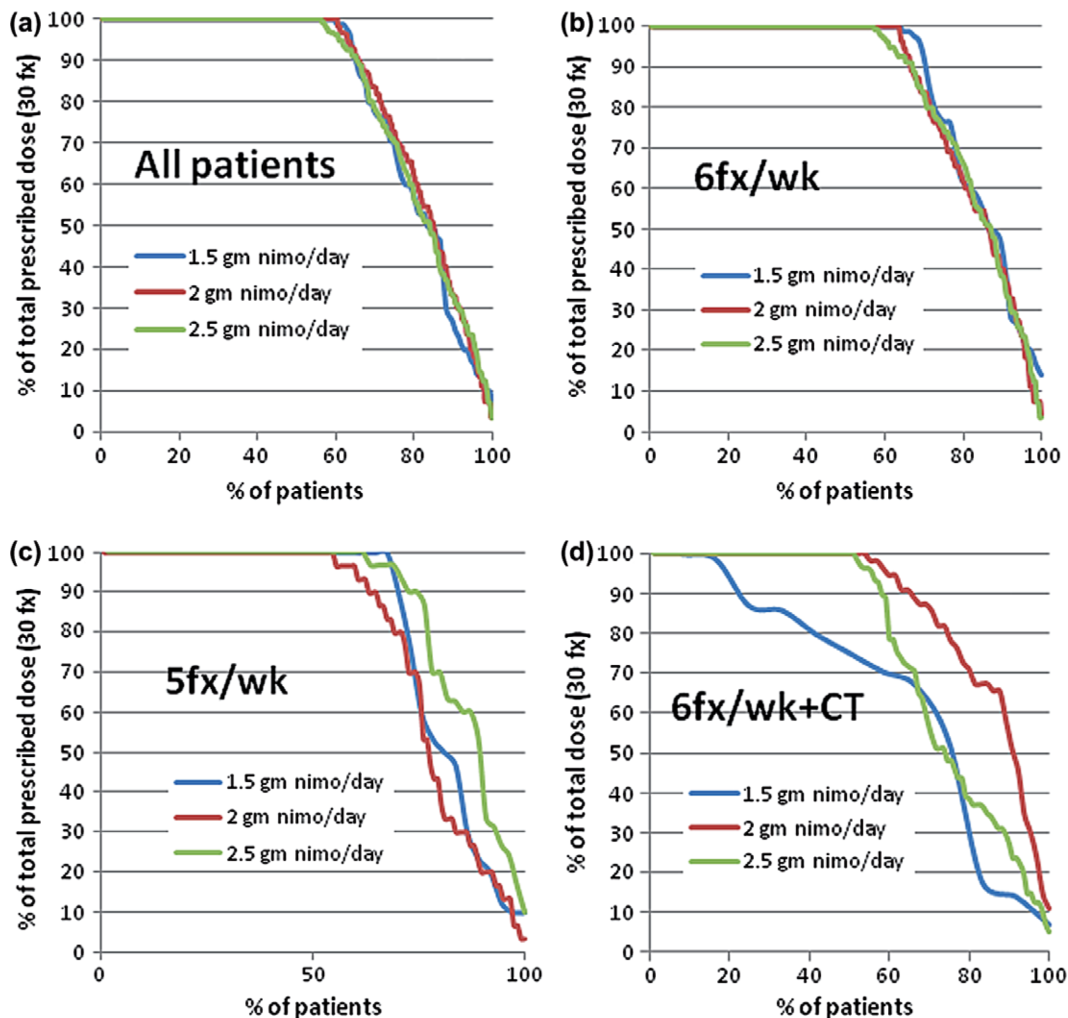

Figure 3. The relation between the percentage of patients and the percentage received of the full prescribed dose (as a function of daily given dose). (a) In all patients. (b) In the accelerated fractionation treatment group. (c) In the conventional fractionation treatment group. (d) In the accelerated fractionation + chemotherapy treatment group. CT, chemotherapy; fx, fractions; wk, week.

as an endpoint, female patients were significantly more likely to have dose reduction (OR 2.02; 95% CI 1.50–2.70). The age of the patient was also a significant pretreatment factor associated with dose reduction; patients aged more than 70 years were significantly more likely to have dose reduction. The total given dose was unrelated to side effects, whereas the dose per m^2 of the body surface area was found to be an important factor, and patients who received less than 1100 mg/m^2 were significantly less likely to have dose reduction (OR 0.58; CI 0.44–0.78) compared to those who received 1100–1300 mg/m^2, but with no statistically significant difference between those received $>$ 1300 mg/m^2 and those who received 1100–1300 mg/m^2. The tolerance was also less in the group of patients receiving accelerated chemo-radiotherapy (OR 1.70; CI 1.20–2.50).

A similar logistic regression analysis using severe nausea and vomiting is also presented in Table III. Female patients were significantly more likely to have nausea and vomiting whereas patients with advanced stage (stage III–IV) were significantly less likely to have nausea and vomiting. The dose response relationship was also found for this endpoint, and patients who received a daily dose less than 1100 mg/m^2 were significantly less likely to have nausea/vomiting than those who received a daily higher dose/m^2.

Accelerated chemo-radiotherapy was also found to be statistically significant treatment-related factor with patients are more likely to have severe nausea and vomiting (OR 2.09; CI 1.40–3.10).

Discussion

Nimorazole is a 5-nitroimidazole compound [3,21]. It has been used as a hypoxic radiosensitizer due to its high electron affinity enabling the drug to mimic the effect of oxygen in rendering hypoxic cells radio-sensitive [1,22,23]. In single doses it reaches lower levels than the more potent 2-nitroimidazoles (e.g.

Table III. Univariate and multivariate logistic regression models to identify covariates that are associated with dose reduction and nausea/vomiting.

	Dose reduction				Nausea/vomiting			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Covariates	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age								
≤40 years	1.50 (0.59–3.80)	0.383	1.65 (0.64–4.20)	0.296	1.80 (0.71–4.90)	0.199		
41–50 years	1.26 (0.86–1.80)	0.228	1.23 (0.83–1.84)	0.288	1.20 (0.80–1.79)	0.364		
51–60 years	1		1		1			
61–70 years	1.18 (0.87–1.59)	0.265	1.19 (0.87–1.60)	0.268	0.77 (0.56–1.06)	0.112		
>70 years	1.67 (1.14–2.45)	0.008	1.87 (1.25–2.80)	0.002	1.13 (0.75–1.69)	0.547		
Sex								
Male	1		1		1			
Female	1.77 (1.34–2.34)	0.000	2.02 (1.50–2.70)	0.000	1.64 (1.20–2.20)	0.001	1.74 (1.27–2.37)	0.000
Performance WHO								
0–1	1				1			
2–3	1.29 (0.79–2.10)	0.307			0.99 (0.59–1.68)	0.989		
Stage								
I–II	1		1		1		1	
III–IV	1.20 (0.95–1.50)	0.109	1.12 (0.81–1.50)	0.477	0.50 (0.38–0.65)	0.000	0.39 (0.27–0.55)	0.000
Dose/day								
1500 mg	1				1			
2000 mg	0.97 (0.65–1.44)	0.890			0.86 (0.57–1.29)	0.490		
2500 mg	1.15 (0.76–1.72)	0.492			0.89 (0.59–1.35)	0.598		
Dose/m^2								
<1100 mg/d	0.65 (0.50–0.86)	0.002	0.58 (0.44–0.78)	0.000	0.82 (0.62–1.08)	0.176	0.72 (0.54–0.97)	0.032
1100–1300 mg/d	1		1		1		1	
>1300 mg/d	1.53 (0.78–3.0)	0.211	1.70 (0.84–3.30)	0.129	0.45 (0.19–1.03)	0.061	0.54 (0.23–1.20)	0.163
Treatment group								
5 fx/wk	1.09 (0.79–1.50)	0.589	1.09 (0.76–1.57)	0.612	1.61 (1.16–2.23)	0.004	1.05 (0.73–1.50)	0.776
6 fx/wk	1		1		1		1	
6 fx/wk+CT	1.60 (1.16–2.23)	0.004	1.70 (1.20–2.50)	0.003	1.26 (0.89–1.70)	0.179	2.09 (1.40–3.10)	0.000

CT, chemotherapy; Fx, fractions.

misonidazole). However, in fractionated clinical treatments, the same tumor sensitization can be achieved, due to lack of severe neurotoxicity and better tumor/plasma ratios [3,19–25].

Hypoxic modification of radiotherapy has shown clinical benefit in the treatment of HNSCC and to some extent in other squamous cell carcinomas such as uterine cervix carcinoma [1,26]. Thus, nimorazole has been adapted for routine clinical use in head and neck cancer patients in Denmark since 1990, due to the outcome of the DAHANCA 2 [7] and DAHANCA 5 [9] studies which both demonstrated the benefit of hypoxic modification in non-glottis larynx and pharynx cancer. Whereas the use of misonidazole in the DAHANCA 2 trial resulted in unacceptable neurotoxicity [7,8], did the DAHANCA 5 study conclude that nimorazole significantly improves the effect of radiotherapeutic management of supraglottic and pharynx tumors and can be given without major side effects [9,10]. Since the routine introduction of nimorazole in Danish guidelines no further studies have focused on the drug toxicity and patients compliance to the prescribed dose, although it was prospectively recorded in the DAHANCA database.

In the DAHANCA-5 study 51% of the patients achieved the planned drug treatment [9,10]. The current study shows that the compliance of patients with the full prescribed dose was 58%. Most of the patients, who ceased nimorazole treatment, did so due to drug side effects (93% of the causes of dose reduction). The most reported side effect being nausea/vomiting (87% of the known side effects), which is consistent with the original report [9,10]. The less frequent side effects that caused dose reduction were skin rash or flushing. All side effects were transient, with rapid improvement after the cessation of the drug and there were neither reported serious nor late side effects.

A few other studies have evaluated the toxicity of nimorazole in the treatment of HNSCC. In a phase I study [25] on 22 patients to evaluate the toxicity of adding nimorazole to the continuous hyperfractionated accelerated radiation therapy (CHART regimen), nimorazole was administered before radiotherapy at a dose of 1.2 g/m^2 with the

first daily fraction. Seventeen patients received a further 0.6 g/m^2 before each second daily fraction and six of these patients received an additional dose of 0.6 g/m^2 before each third fraction. They found that the drug toxicity was limited to nausea and vomiting apart from two cases of mild paraesthesia at the highest dose level. In the corresponding phase II study [27] where 61 patients have included, nimorazole was administered at a dose of 1.2, 0.9, and 0.6 g/m^2 with the first, second and third daily fractions, respectively. Grade 3 nausea or vomiting occurred in 22% of patients. Two patients developed grade 1 peripheral neuropathy, and one patient died during treatment of encephalopathy, which was considered an idiosyncratic reaction to the drug.

A case study on two patients with head and neck cancer [28] suggested an interaction between nimorazole and the vitamin K antagonists (phenoprocoumon). This observation was supported by the previously reported inhibitory effect of the other 5-nitroimidazole (metronidazole) on CYP2C9, which metabolizes vitamin K antagonists [29]. This should be put in consideration when treating patients who receive vitamin K antagonists, when these patients undergo nimorazole treatment.

The most relevant pretreatment factor associated with dose reduction was gender (female patients were more likely to have dose reduction than males). The observation that patients with advanced stage III–IV disease had less complaints of mild to moderate nausea/vomiting (not causing dose reduction), should probably be seen in the light of a more prominent burden of other symptoms directly related with the disease and radiotherapy treatment. Therefore only the complaints, but not the compliance to Nimorazole were influenced.

Our study has several potential limitations that should be discussed. Although our data in principle should have been prospectively recorded in the DAHANCA database, this was rather incomplete and consequently supplemented with retrospective data obtained through medical record review. Thus, there were some problems of missing and conflicting data [30] which could not be retrospectively retrieved. Also, inter-observer reliability or reproducibility in the medical record abstraction process may affect precision and accuracy [30,31]. The data were collected from different DAHANCA trial periods [17], each of which had somewhat different eligibility criteria, radiotherapy regimen, and some variations in the recording of compliance and side effects in the database. Especially in the combined treatment schedules where patients were given both cisplatin and nimorazole, it was extremely difficult retrospectively to determine if the incidence of side effects (particularly nausea and vomiting) was the result of nimorazole treatment itself, unless it was noted in patient's chart that the side effect improved after cessation of the drug. Importantly, it should be remembered that for most patients with head and neck cancer, the highest priority is cure and length of survival [32]. Excessive concern about acute and not life-threatening treatment toxicity should not prevent the use of such effective and tolerable drug, provided the patient is well informed about the potential side effects.

In conclusion, nimorazole is a fairly tolerable drug in head and neck cancer patients, with mild to moderate acute, but neither persistent nor late, toxicity. It can be administered with chemotherapy and different radiotherapy fractionation schedules without major effect on toxicity or compliance.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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