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Nimorazole as a hypoxic radiosensitizer in the treatment of supraglottic larynx and pharynx carcinoma. First report from the Danish Head and Neck Cancer Study (DAHANCA) protocol 5-85

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Summary

Between January 1986 and September 1990, 422 patients with pharynx and supraglottic larynx carcinoma were randomized to receive the hypoxic cell radiosensitizer nimorazole (NIM) or placebo in association with a course of conventional primary radiotherapy. A preliminary analysis including the first 288 patients showed that the stratification parameters were significant (3-year actuarial local-regional tumor control, $p < 0.05$) for sex (females 52% vs males 34%), tumor size (T1–T2 47% vs T3–T4 32%) and pre-irradiation hemoglobin (Hb) concentration (high 41% vs low 34%). Overall, the NIM group showed a significantly better local-regional control rate than the placebo group (46% vs 32%). There was an apparent additive effect of Hb concentration and NIM. Thus, in the male group, placebo patients with low Hb had a 23% control rate compared to 46% in NIM treated patients with Hb above 9 mmol/l ($p < 0.05$). The similar effect in females could not be evaluated due to the small number of women with this disease. NIM was well tolerated and drug-related side effects were minor and tolerable, with transient nausea and vomiting as the most frequent complication. A final conclusion of the study must await an evaluation including all patients and a longer observation time.

Introduction

Between 1979 and 1985, a randomized trial, evaluating the hypoxic cell radiosensitizer misonidazole in the treatment of larynx and pharynx carcinoma (DAHANCA-2), was performed by the Danish Head and Neck Cancer Study Group [9]. Although no overall significant benefit appeared, there was a significant improvement in the strata which included patients with pharynx tumors. A similar tendency was also observed in patients with supraglottic larynx carcinoma, whereas patients with glottic lesions did not show any benefit. Furthermore, the study revealed that patients with a low hemoglobin value had a significantly

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poorer prognosis if they belonged to the groups which also showed a benefit from misonidazole. The hemoglobin and misonidazole effects seem to be independent and probably additive. Unfortunately, misonidazole induced significant peripheral neuropathy in 26% of the patients, and it was concluded that it therefore is unsuitable for further clinical use [4,9].

On this basis, it was decided to evaluate the less toxic hypoxic radiosensitizer nimorazole (1-(N-β-ethyl-morpholine)-5-nitro-imidazole; NIM) in pharynx and supraglottic larynx tumors. This drug has previously been evaluated in preclinical and clinical phase I and II studies [7,8,11] and has so far not demonstrated any significant toxicity except transient nausea and vomiting. Although the sensitizing ability is less than what theoretically can be achieved by misonidazole, the drug shows a flat dose response curve, implying that at clinically relevant doses the hypoxic radiosensitizing ability is fairly high, approximately 1.3 [7]. Furthermore, the drug can be given in association with a conventional radiation therapy schedule and was therefore found suitable for use in the new study.

The observation that a low hemoglobin value was associated with a poor local control was in agreement with numerous other studies [1,5,6]. A few small clinical trials have indicated that blood transfusion given to patients with low hemoglobin values may increase the tumor control probability in patients with carcinoma of the uterine cervix [1,6]. This question was therefore also addressed in the current study, by randomizing patients with low hemoglobin values to ± blood transfusion, prior to inclusion in the NIM trial.

The present analysis gives the first (preliminary) report from the trial and will especially focus on the study design, drug compliance and toxicity.

Protocol design and patient allocation

The Danish Head and Neck Cancer Study Protocol 5-85 was activated in January 1986 as a multicentre, randomized and balanced double-blind trial with the object:

1) to assess the efficacy of nimorazole, given as a hypoxic radiosensitizer in conjunction with radiotherapy of invasive carcinoma of the supraglottic larynx and pharynx.

2) to assess the tolerance and toxicity of nimorazole.

3) to assess the influence of hemoglobin concentration on the tumor response to irradiation.

The trial is a double-blind study in which the control group receives placebo, instead of NIM. The study design, stratification and randomization arms are shown in figure 1.

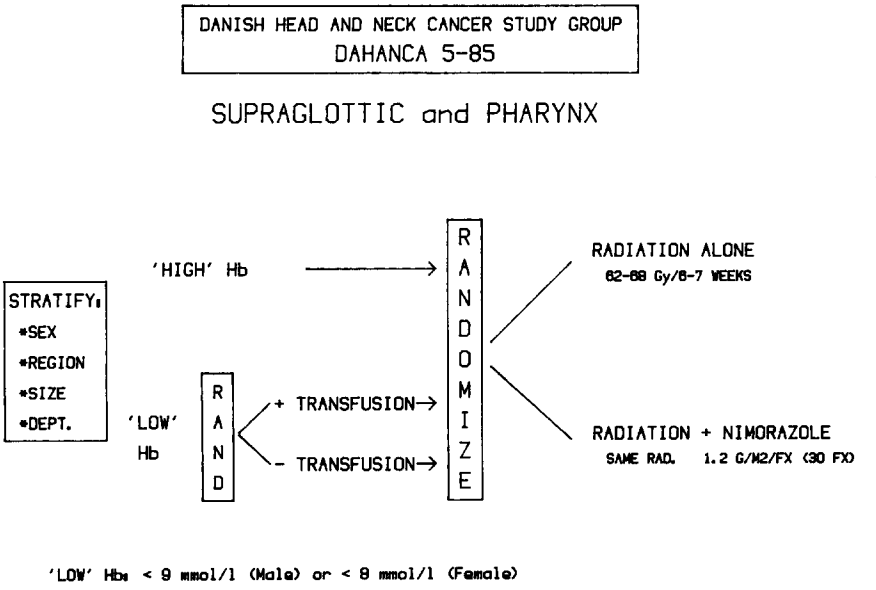

Fig. 1. Schematic representation of trial design and randomization procedure for the Danish Head and Neck Cancer Study protocol 5-85.

From January 1986 to September 1990, 422 patients have been included. The intake has been rather steady throughout the period. The criteria for eligibility were invasive squamous cell carcinoma of the supraglottic larynx (T2–T4, UICC 1982) or pharynx (T1–T4), no evidence of distant metastases, normal liver and renal function and no neurological disorders expected to interfere with the drug treatment. The study was designed according to the Helsinki Declaration II, and was approved by the local ethical committees. Prior to randomization the patients were stratified according to sex, institution, tumor site (supraglottic vs. pharynx), tumor status (T1–T2 vs. T3–T4) and hemoglobin concentration. They were then randomised to radiotherapy with NIM or placebo.

NIM (or placebo) was given 90 min prior to irradiation during the first 30 fractions. The dose per fraction was 1.2 g/m^2 corresponding to 36 g/m^2 total. The dose and drug-irradiation interval was based on prior pharmacokinetic toxicological evaluation [8,11].

Radiotherapy was given with Co-60 or 4 MeV photons, using parallel opposed fields. Electrons may be applied to the neck in order to reduce spinal cord dose. The treatment was applied according to standardized fields, including primary tumor and involved lymph nodes. A tumor dose of 62–68 Gy (2 Gy per fraction, 5 fractions per week) was applied. The dose depended of tumor size, with larger tumors receiving the largest dose. The fields included the first non-involved lymph node station, but after 50 Gy the fields were reduced to include only primary macroscopically known tumors.

Patients with low pre-irradiation hemoglobin (females < 8 mmol/l, males < 9 mmol/l) were randomized to $\pm$transfusion, prior to final randomization to the hypoxic sensitizer. Patients randomized to transfusion were given packed red blood cells to achieve a hemoglobin concentration in the "high" value range.

Results

Of the 422 included patients, 288 had completed treatment with at least 3 months additional follow up (per October 31, 1989). These patients were included in the current analysis. The results must be regarded as preliminary, and longer observation times together with an analysis including all patients are required, before a final conclusion can be drawn from the study.

Distribution as a function of the stratification group followed the expected pattern (Table I) and no significant differences were found between the NIM and the placebo group.

Drug tolerance and toxicity

Tolerance to NIM/placebo could be evaluated in 277 patients. The results are seen in Table II and show that no severe side effects were observed. Most 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 have been found including one patient with sign of impaired liver

Table 1. Distribution according to stratification group (288 patients included in analysis)

Stratification group		Nimorazole (144 pts)	Placebo (144 pts)	All (288 pts)
Sex	Females	35 (12%)	37 (13%)	72 (25%)
	Males	109 (38%)	107 (37%)	216 (75%)
Region	Supraglottic	48 (17%)	46 (16%)	94 (33%)
	Pharynx	96 (33%)	98 (34%)	194 (67%)
Size	T1–T2	62 (22%)	66 (23%)	128 (45%)
	T3–T4	82 (28%)	78 (27%)	160 (55%)
Hemoglobin	High	83 (29%)	87 (30%)	170 (59%)
	Low	61 (21%)	57 (20%)	118 (41%)
	Transfused	32 (11%)	25 (9%)	57 (20%)
	Not transfused	29 (10%)	32 (11%)	61 (21%)

Table 2. Drug compliance and toxicity (277 patients)

Toxicity/compliance	Nimorazole (136 pts)	Placebo (141 pts)	All (277 pts)
Completed as scheduled	78 (57%)	112 (79%)	190 (69%)
Toxicity	41 (30%)	15 (11%)	53 (19%)
Nausea/vomiting	23 (12) *	10 (3)	33
Impaired liver functions	1 (1)	–	1
Neurological symptoms	4 (2)	–	4
Skin rash	5 (2)	1 (0)	6
Flushing	7 (6)	3 (2)	10
Other	1 (0)	1 (1)	2
Other non-compliance	17 (13%)	14 (10%)	31 (11%)
Problems with swallowing	7 (5)	10 (10)	17
Treatment not completed	10 (10)	4 (4)	14
Patients refusal or risk of toxicity. (no symptoms)			

* Treatment not completed: Nimorazole 38 pts (28%); Placebo 20 pts (14%).

function, but this patient probably also had metastases to the liver. The influence of NIM on this side effect was questionable. The few cases of neurological symptoms were also dubious. A total of 30% of the patients receiving active NIM treatment showed some form of side-effects, however, none of these were severe and as a whole NIM has demonstrated an absence of important toxicity. No relationship between sex or given drug dose has been found. Also 10% of the placebo patients indicated side-effects. Thus, the toxicity has so far been acceptable and was expressed in the form of acute and reversible changes which have caused no major discomfort to any of the patients.

Both radiotherapy and drug treatment were relatively well tolerated. Compliance with radiotherapy was the same in both treatment groups, and 93% of the patients completed the planned treatment. Compliance with drug treatment was dependent on whether the patient received NIM or placebo, especially due to the increased gastrointestinal toxicity in the NIM group. As a whole, 65% of the patients achieved the planned drug treatment (NIM 56%, placebo 72%), and 75% achieved more than 25 drug treatments (NIM 68%, placebo 81%). The major cause of failure to fulfill the treatment was due both to the acute toxicity and, to a large extent, to the patients' refusal or his difficulties in swallowing the large capsules (NIM 11%, placebo 10%). Thus, in only 17% of the NIM patients and 4% of the placebo patients has the treatment ceased, due to direct toxicity.

Plasma nimorazole

Routine pharmacokinetic analysis has been performed in all patients during the initial treatment with NIM. Multiple plasma samples have been taken during the first 6-8 hours in order to get information about the pharmacokinetic properties of the drug. The plasma concentrations were measured on HPLC as

Table 3. Local-regional control (3-year actuarial value) as a function of stratification group (288 patients)

Sex:	Females	(72)	$52\% \pm 8^{+}$
	Males	(216)	$34\% \pm 5^{+}$
Region:	Supraglottic	(94)	$41\% \pm 7$
	Pharynx	(194)	$36\% \pm 5$
Size:	T1–T2	(128)	$47\% \pm 6^{+}$
	T3–T4	(160)	$32\% \pm 5^{+}$
Hemoglobin:	High *	(170)	$41\% \pm 5^{+}$
	Low	(118)	$34\% \pm 6^{+}$
	Transfused	(57)	$39\% \pm 8$
	Not transfused	(61)	$32\% \pm 8$

* Females < 8, males < 9 mmol/l

\+ $p < 0.05$

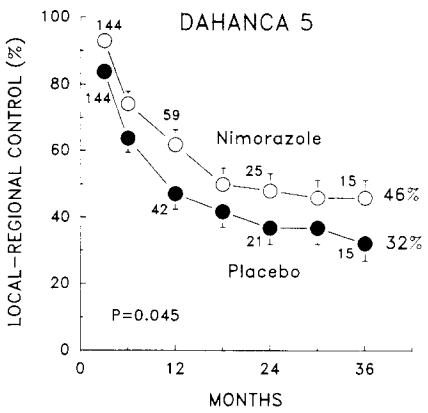

Fig. 2. Actuarial estimated local-regional tumor control in patients randomized to receive nimorazole or placebo in conjunction with conventional radiotherapy for carcinoma of the pharynx and supraglottic larynx.

previously described [7,8]. This analysis has not yet been completed but some information exists on the first 140 patients treated with NIM.

The peak plasma concentration ranges from 18–84 mg/l with a median value of 33. In most patients the peak plasma concentration is achieved within 90 min after intake of the capsules, but a considerable variation in absorption times has been found. This has furthermore been associated with the peak plasma concentrations and there is a significant decrease in peak concentration with increasing peak time. A total of 61% of the patients have obtained peak plasma values above 30 mg/l which must be considered satisfactory and – with the exception of 33 patients, where peak absorption times occurred later than 2.5 hours after intake – all observations have been as expected.

Tumor response

In the following, only local-regional control data will be given. This because local-regional tumor control is the dominating parameter in these patients and reflects the cancer related survival, and also because the observation time has been relatively short. The tumor responses were estimated as 3-year actuarial local-regional control probability and comparisons were calculated by log-rank analysis.

Based on the previous study, the stratification parameters in the DAHANCA-5 protocol were chosen to select equally balanced groups with distinct prognostic parameters. Table III shows the 3-year tumor control as a function of the stratification group, and it is apparent that well-known parameters such as sex, T-classification, and hemoglobin concentration in the current study are parameters of prognostic significance. On the other hand, patients with supraglottic larynx cancers do not seem to differ from patients with pharynx tumors, a parameter which also appeared from the previous study.

Overall, patients randomized to NIM showed a better local-regional control rate than the placebo group (figure 2). This difference is statistically significant, but requires further observation time to be established as conclusive.

The relationship between tumor response, NIM, and hemoglobin concentration was investigated in male patients. Figure 3 shows that both a high hemoglobin concentration and the presence of NIM were good prognostic parameters, and a significant difference was observed between males with high hemoglobin who were treated with NIM versus patients with low hemoglobin who received placebo (46% versus 23%). More patients and time are needed to establish this phenomenon.

Discussion

The current study shows an improvement in the tumor control when compared to the similar patient group in the DAHANCA 2 trial [9]. Although this may not solely be due to the use of NIM, but (partly) also be a consequence of changing the radiotherapy schedule from split-course to continuous irradiation, it

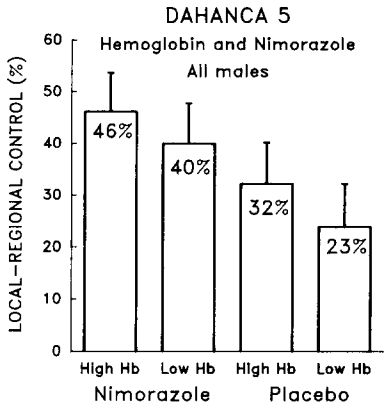

Fig. 3. Actuarial estimated local-regional tumor control in male patients as a function of nimorazole or placebo and pre-treatment hemoglobin.

does demonstrate the usefulness of pursuing a constant policy within the nation-wide DAHANCA study group.

No important or chronic toxicity has been noted with the use of NIM and the drug response and compliance are in agreement with the previous phase I and II studies [8,11].

The tumor response benefit in favour of NIM appears promising. Although preliminary, the results are further encouraged by the observation that an apparent independent and additive relationship exists between the use of the hypoxic radiosensitizer and the hemoglobin concentration. This is in agreement with the DAHANCA-2 trial: a striking similarity between the two studies has appeared [9]. It is remarkable that the Danish head and neck cancer studies so far have been the only large randomized clinical trials which have shown an apparent benefit from the use of hypoxic radiosensitizers [2,6]. There is substantial evidence from hyperbaric oxygen trials, measurements of oxygen concentrations in tumors, and the relationship between hemoglobin concentration and tumor control, which indicates that hypoxia may be a critical factor when treating carcinomas of the head and neck by radiotherapy [3,6]. However, the experience has also pointed towards a substantial heterogeneity within tumors of the same size, site, and histopathology [6,9,10]. It is likely that only in large and homogeneous clinical trials such differences can be detected.

The current DAHANCA-5 study has utilized the experience from the previous clinical trial, in order to further identify patients with a hypoxia problem. In addition it represents the two Danish head and neck clinical trials, the largest randomized studies performed with hypoxic radiosensitizers in head and neck carcinoma, so far. Furthermore, no selection has been performed within the patient group, since all patients with head and neck carcinomas are treated within the few oncological centres in the country. In principle, all Danish patients who fulfill the eligibility criteria should have been included.

The relationship between hemoglobin and tumor response is intriguing. It is obvious that hemoglobin by itself may not reflect the true oxygen status of the tumor, partly due to variations in tumor blood flow and partly because the oxygen unloading capacity of the blood may differ widely [5]. The latter may especially be a consequence of smoking habits. Since almost all patients with head and neck carcinomas are smokers (also during radiotherapy), variations in oxygen availability may be as large as 50% in patients with the same hemoglobin value. An analysis of this problem is in progress. The protocol also addresses the question related to transfusion of low hemoglobin patients to a high hemoglobin level. Whether this will be a successful procedure remains to be analyzed. This will require a more detailed study of the hemoglobin level in transfused patients, and this was not performed in the current analysis.

It should be emphasized that the current analysis is preliminary, and a longer observation time and more patients are needed to reach a final conclusion. In addition, a multivariate analysis may be required to clarify the complexity of various prognostic parameters, but the likely importance of hypoxia seems apparent and further attempts towards overcoming this problem appear to be relevant.

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