CENTER FOR CLINICAL GUIDELINES | CANCER

Nimorazole

Treatment with the hypoxic radiosensitizer Nimorazole in squamous cell carcinoma of the head and neck

Version 2.0

APPROVED
Content
October 6th 2020 (DAHANCA)
Form
January 14th 2021 (Center for Clinical Practice Guidelines | Cancer)

REVISION
Planned: October 6th 2025

INDEXING
DAHANCA, Head and Neck Cancer, Hypoxia, Hypoxic modification, Radiotherapy, Quality Assurance, Nimorazole.

Content

Background

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Clinical Registries (RKKP). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high quality cancer care across the Danish healthcare system. The guideline content is approved by the disease specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The target users of this guideline are health care professionals working in the Danish healthcare system. The guideline consists of systematically prepared statements that can be used as a decision-making support tool by healthcare professionals and patients, when deciding on appropriate and correct care in a specific clinical situation.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome and sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The clinical practice guideline contains central recommendations (chapter 1) and a description of the scientific evidence (chapters 3+4). Recommendations marked A are the strongest, whereas recommendations marked D are the weakest. For further information on strength of evidence see the"Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. Please see the table of contents for page reference.
Information on the national integrated cancer pathways – descriptions of the patient journey through the healthcare system – can be accessed at the Danish Health Authority website: https://www.sst.dk/en

Development of this clinical practice guideline has been funded by The Danish Health Authority (National Cancer Plan IV) and the Danish Clinical Registries (RKKP).

1. Anbefalinger - DA (Quick Guide)

1. **Den hypoxiske strålesensitizer Nimorazol anvendes konkomitant med kurativt intenderet ekstern strålebehandling/kemostrålebehandling af planocellulært carcinom i larynx (excl stadium I glottisk tumor), pharynx, cavum oris og sinonasal regionen (A).**

2. **Nimorazol skal gives 90 minutter (+/- 30 min) før hver strålebehandlingsfraktion. Dosis er ca. 1,2g/m2 kropsoverflade. I forbindelse med en yderligere anden daglig fraktion gives en reduceret dosis på 1 g uafhængigt af kropsoverflade (A).**

3. **Kvalme, som er den hyppigste bivirkning til nimorazol, bør behandles maksimalt antiemetisk forud for evt. seponering (D).**

4. **Genprofilering (herunder hypoxisk status), kan være en relevant del af udredningen på den diagnostiske biopsi (B).**

Recommendations - ENG (Quick Guide)

1. **The hypoxic radiosensitizer nimorazole is indicated concurrent with curatively intended radiotherapy/chemo-radiotherapy of squamous cell carcinomas in the larynx (except stage I glottic tumors), pharynx, oral cavity and sinonasal cavity (A).**

2. **Nimorazole is administered orally 90 minutes (+/- 30 minutes) prior to each scheduled irradiation fraction. The scheduled dose is approximately 1,200 mg (1.2g)/m^2 body surface. In case of two daily scheduled fractions, the dose administered prior to the second fraction is reduced to 1,000 mg (1 g) independently of body surface (A).**

3. **Nausea and vomiting, which are the most common side effects to nimorazole, should be comprehensively treated with antiemetic drugs prior to possible discontinuation of nimorazole (D).**

4. **Gene profiling (including hypoxic status) can be a relevant addition to analysis of the diagnostic biopsy (B).**

2. Introduction

Objective

The overall objective of this guideline is to support high quality cancer care across the Danish healthcare system.
The specific objective is to modify hypoxia-induced radioresistance by optimization and individualization of radiotherapy among patients with squamous cell carcinoma of the head and neck.

Target population

This guideline applies to patients with macroscopic squamous cell carcinoma in the larynx (except stage I glottic tumors), pharynx, oral cavity and sinonasal region. With tumor in these locations DAHANCA recommends addition of concurrent nimorazole to planned curatively intended (chemo-)radiotherapy.

Target User

This guideline has been developed with the aim of supporting clinical decision-making and quality improvement. Thus, the target users are healthcare professionals working in Danish cancer care. The primary target group of this guideline is physicians and nurses involved in the radiation treatment of patients with head and neck squamous cell carcinoma.

3. Scientific evidence

1. **The hypoxic radiosensitizer nimorazole is indicated concurrent with curatively intended radiotherapy/chemo-radiotherapy of squamous cell carcinomas in the larynx (except stage I glottic tumors), pharynx, oral cavity and sinonasal cavity (A).**

2. **Nimorazole is administered orally 90 minutes (+/- 30 minutes) prior to each scheduled irradiation fraction. The scheduled dose is approximately 1,200 mg (1.2g)/m^2 body surface. In case of two daily scheduled fractions, the dose administered prior to the second fraction is reduced to 1,000 mg (1 g) independently of body surface (A).**

Literature review and evidence description

The background for The Danish Head and Neck Cancer Group's (DAHANCA) recommendation is the double-blinded randomized prospective phase III study DAHANCA 5 (1). The study included 442 (414 eligible) patients and showed a significantly improved loco-regional control rate (49 versus 33%, p=0.002) when conventional primary radiotherapy was supplemented with concurrent nimorazole compared with placebo (no nimorazole). Disease specific survival was also significantly improved (OR 1.92(1.30-2.84)), whereas only an insignificant trend toward improved overall survival was found (1)[1b].
Subsequent meta-analyses have substantiated the relevance of hypoxic modulating treatment in addition to radiotherapy with regard to locoregional control, disease specific survival and overall survival (2, 3) [1a].
See Appendix 1 for details on dose and administration.

Rationale

Since nimorazole was introduced as part of the standard radiotherapy regimen in most cases of HNSCC, treatment has been modified and optimized with accelerated fractionation and concurrent chemotherapy, which, along with the implementation of IMRT, have improved the overall treatment response even further (4-6). The effects of these different radiobiological modifications are largely independent and multivariate analysis of the patients in DAHANCA clinical trials (6) showed an individual effect of nimorazole independent of accelerated fractionation and chemo-radiotherapy, with an adjusted hazard ratio for loco-regional tumor control of 0.64 (0.52-0.80) (7).

3. **Nausea and vomiting, which are the most common side effects to nimorazole, should be comprehensively treated with antiemetic drugs prior to possible discontinuation of nimorazole (D).**

Literature review and evidence description

This recommendation is based on good clinical practice and consensus among the working group/DAHANCA since there has been no prospective clinical studies exploring the use of antiemetic drugs preceding discontinuation of nimorazole.

Pharmacokinetics, compliance, side effects and tolerance have been thoroughly examined in a PhD-study (8). The conclusion from this study was, that nimorazole basically can be administered concurrently to chemo- and radiotherapy but at the cost of (mainly) acute reversible side effects. This results in relatively low compliance to nimorazole and it was found, that only around 60 % of patients completed the full extent of the prescribed nimorazole dose during the radiotherapy course. The main side effect and reason for discontinuation was nausea and vomiting but it was observed that all side effects ceased quickly after discontinuation (9, 10)[2b].

Patient values and preferences

The main side effects to nimorazole are nausea and vomiting. This can be problematic considering the intensive (chemo-) radiation treatment where the nutritional status is often compromised.

Rationale

To ensure the best outcome of the treatment for every individual patient, optimal supportive treatment is recommended if nausea and vomiting occurs during treatment. If optimal supportive care is not sufficient, nimorazole should be discontinued. This is based on the rationale that the patient should receive treatment with the best obtainable effect, but only at the cost of acceptable side effects. For more details on side effects and administration, see Appendix 1.

4. Gene profiling (including hypoxic status) can be a relevant addition to analysis of the diagnostic biopsy (B).

Literature review and evidence description

Hypoxic gene profiling has been shown to be predictive for the use of nimorazole (11) and is thought to enable optimization of the treatment for the individual patient and provide information beyond already known tumor characteristics (TNM, differentiation grade, etc).
In an evaluation of the cohort in DAHANCA 5 hypoxic gene profiling has enabled differentiation between responders and non-responders to nimorazole (12)[2b]. Data from a prospective randomized multicenter study (however incomplete due to poor recruitment) supports the relevance of hypoxic modification with nimorazole in cases of more hypoxic tumors assessed by hypoxic gene expression (13)[1b]. Another prospective randomized placebo-controlled trial investigates the hypoxic gene feasibility but has not yet been published (14)[1b].
Since nimorazole is often discontinued due to side effects during the course of radiotherapy, DAHANCA finds it relevant to add hypoxic gene profiling to the primary work-up. The rationale is to identify patients with expected benefit of the drug in order to optimize the supportive medical treatment before potential discontinuation.

Currently it is not possible to omit nimorazole based on the hypoxic gene profile, however with the ongoing non-inferiority DAHANCA 30-study (NCT02661152) it is aimed to investigate whether treatment with nimorazole can be avoided among patients with less hypoxic HNSCC without increasing the risk of treatment failure for these patients.

Comments and considerations

For information on administration, dose, side effects and interactions, see Appendix 1.

4. Reference list

1. Overgaard J, Hansen HS, Overgaard M, Bastholt L, Berthelsen A, Specht L, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DAHANCA) Protocol 5-85. Radiother Oncol. 1998;46(2):135-46.
2. Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck--a systematic review and meta-analysis. Radiother Oncol. 2011;100(1):22-32.
3. Overgaard J. Clinical evaluation of nitroimidazoles as modifiers of hypoxia in solid tumors. Oncol Res. 1994;6(10-11):509-18.
4. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet (London, England). 2003;362(9388):933-40.
5. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol. 2011;100(1):33-40.
6. Baumann M, Krause M, Overgaard J, Debus J, Bentzen SM, Daartz J, et al. Radiation oncology in the era of precision medicine. Nat Rev Cancer. 2016;16(4):234-49.
7. Overgaard J. Improving radiotherapy of squamous cell carcinoma of the head and neck (HNSCC) through a continuous process of biological based clinical trials − a 40-year experience from the Danish Head and Neck Cancer Group – DAHANCA. Eur J Cancer. 2017.
8. Metwally MA. PhD dissertation: Nimorazole as a hypoxic radiosensitizer in the radiation treatment of head and neck squamous cell carcinoma. Health Aarhus University. 2015.
9. Metwally MAJJAO, J. Study of the Population Pharmacokinetic Characteristics of Nimorazole in Head and Neck Cancer Patients Treated in the DAHANCA-5 Trial. Clin Oncol (R Coll Radiol). 2015.
10. Metwally MA, Frederiksen KD, Overgaard J. Compliance and toxicity of the hypoxic radiosensitizer nimorazole in the treatment of patients with head and neck squamous cell carcinoma (HNSCC). Acta Oncol. 2014;53(5):654-61.
11. Toustrup K, Sorensen BS, Nordsmark M, Busk M, Wiuf C, Alsner J, et al. Development of a hypoxia gene expression classifier with predictive impact for hypoxic modification of radiotherapy in head and neck cancer. Cancer Res. 2011;71(17):5923-31.
12. Toustrup K, Sorensen BS, Lassen P, Wiuf C, Alsner J, Overgaard J, et al. Gene expression classifier predicts for hypoxic modification of radiotherapy with nimorazole in squamous cell carcinomas of the head and neck. Radiother Oncol. 2012;102(1):122-9.
13. Metwally MAG, C.; Overgaard, J.; et al. IAEA-HypoX. A randomized multicenter study of the hypoxic radiosensitizer nimorazole concomitant with accelerated radiotherapy in head and neck squamous cell carcinoma. 2015.
14. Thomson D, Yang H, Baines H, Miles E, Bolton S, West C, et al. NIMRAD - a phase III trial to investigate the use of nimorazole hypoxia modification with intensity-modulated radiotherapy in head and neck cancer. Clin Oncol (R Coll Radiol). 2014;26(6):344-7.

5. Methods

This guideline has been prepared on behalf of DAHANCA in a working group consisting of senior registrar Kasper Toustrup, Prof. Jens Overgaard and Prof. Jesper Grau Eriksen, who collectively have been involved in most of the clinical and basic research that has established the use of nimorazole in Denmark.
The decision to use nimorazole and the implementation of the hypoxic gene profile as a permanent part of the work-up of squamous head and neck cancer has been taken by DAHANCA.

Literature search and Evidence assessment

No formalized literature review has been made, but results from relevant meta-analyses and a recent PhD thesis on nimorazole are the basis for the recommendations in the guideline. Co-authors of the present guideline are the lead authors of the most substantial scientific literature on the subject.

Articulation of the recommendations

The recommendations of the guideline have been phrased by the work group for review in an action-oriented language which reflects the underlying evidence.

Stakeholder involvement

Only the group of authors and DAHANCA have been involved in the preparation of this guideline.

External review and guideline approval

The guideline has been reviewed by DAHANCA preceding approval on the DAHANCA board meeting on the 6th of October 2020.

Recommendations which generate increased costs

None of the recommendations in this guideline are expected to increase expenses.

Need for further research

DAHANCA 30 (NCT02661152) is an ongoing non-inferiority study aiming to determine whether nimorazole can be omitted from standard treatment without deteriorating outcome among patients with a hypoxic profile indicating well-oxygenated HNSCC.
Both NIMRAD (16) (NCT01950689) and EORTC 1219 (NCT01880359) are more recent randomized studies focusing on the effect of hypoxic modification in modern radiotherapy. At present, no data has been published from these studies. With the aim of evaluating the effect of nimorazole including the beneficial factors of modern accelerated chemo-radiotherapy a new confirmatory prospective randomized study is considered.

Authors

- Kasper Toustrup, staff oncologist, MD, Ph.D., Department of Oncology, Aarhus University Hospital.
  Conflict of interest: Co-owner of the patent rights of the hypoxic gene profile.
- Jens Overgaard, Professor and consultant, MD, MDSc., Department of Experimental Clinical Oncology, Aarhus University Hospital.
  Conflict of interest: Co-owner of the patent rights on the hypoxic gene profile.
- Jesper Grau Eriksen, Professor and consultant, MD, Ph.D. Department of Oncology, Aarhus University Hospital.
  Conflict of interest: None.
- English translation by Morten Horsholt Kristensen, MD, Ph.D. student. Department of Oncology, Aarhus University Hospital.
  Conflict of interest: None.

6. Monitoring

Standards and indicators

Information on the administration of nimorazole is registered in the DAHANCA database. Monitoring is continuously ongoing based on quality assurance indicators defined by DAHANCA. Results from this quality assurance is published yearly in cooperation with The Danish Clinical Quality Program– National Clinical Registries (RKKP)

Plan for audit and feedback

A continuous dialogue between the different centers at DAHANCA meetings aims to ensure feedback along with a national quality evaluation report of the clinical parameters in the DAHANCA database published yearly in cooperation with RKKP.

7. Appendix

Appendix 1 – Administration, dose, side effects and interactions

Administration and dose

Nimorazole is administered 90 minutes (+/- 30 minutes) prior to the first of each daily radiotherapy treatment in a dose of approximately 1.2g (1,200mg) per m^2 body surface. In case of accelerated radiotherapy regimen, the second daily dose of only 1g (1,000 mg) is administered independently of body surface. The "treatment schedule" (see below) is handed out to the patient and is continuously filled out during the course of radiotherapy.

The total dose during the radiotherapy course should be approximately 36 g (3,600 mg)/m^2 and should not exceed 40 g/m^2 or a total of 75 g. This dose is expected to result in maximum radiotherapy enhancement ratio and represents the maximal tolerable dose.

Side effects

Potential side effects are registered in the patient record and in the DAHANCA database under the heading "follow-up during treatment"/(Kontrol under behandling).

Most common side effects and treatment options (frequencies from (10):

a. Gastrointestinal symptoms, especially **nausea** and **vomiting** (30% grade 2-3).
    i. Antiemetic drugs can be used, just as the tablets can be taken with a small meal.
    ii. If the patient is still suffering from nausea and vomiting despite maximal antiemetic treatment a break in treatment or dose reduction of nimorazole should be initiated. NB: exclude other causes of nausea and vomiting (irradiation, morphine treatment, chemotherapy, constipation, dehydration, electrolyte imbalance, taste disorders, mucositis, feeding tube, anxiety, pain, etc.)
b. **Flushing** (2%): A subjective sensation of warmth and discomfort, normally without any objective findings (change in blood pressure, etc.). This symptom can occur shortly after administration of nimorazole and will most often spontaneously disappear within minutes or (rarely) hours. The symptoms are transient in nature, hence the patients should, if possible, continue nimorazole treatment despite flushing.
c. **Skin rash** (4%): if patients experience skin rash nimorazole should be discontinued if a causality with nimorazole is suspected.
d. If **paraesthesia** or **peripheral neuropathies** (rare) occur during treatment, discontinuation or a treatment break is recommended. It should be considered that cisplatin may also cause these symptoms.
e. If liver enzymes rise (rare) during treatment with nimorazole, discontinuation should be considered, since the drug is primarily eliminated through hepatic metabolism.

Interactions

To our knowledge, there has been no studies specifically investigating interactions with nimorazole. However, since chemically similar drugs (i.e. metronidazole) might have somewhat similar interactions as nimorazole the following represents an indicative and empirical guideline regarding interactions with nimorazole:
Metronidazole is known to increase the anticoagulative effect of coumarines (such as Warfarin). Combining the use of phenytoin and phenobarbital can accelerate the degradation of metronidazole and thereby reduce the plasma concentration of metronidazole.In contrast, combining the use of cimetidine and metronidazole can reduce the degradation of metronidazole and thereby result in an increase of the plasma concentration of metronidazole.
An acute state of confusion may occur after simultaneous administration of metronidazole and disulfiram (Antabuse), hence this combination of drugs should be avoided.
Certain drugs have potential interactions with nimorazole: especially other nitroimidazoles (metronidazole, misonidazole, pimonidazole etc.) and aminoglycosides (streptomycin, gentamycin, etc.).

NAME..... CPR.....

GUIDELINE IN THE ADMINISTRATION OF NIMORAZOLE TABLETS

From the clinic you have been handed out tablets as part of the treatment (Nimorazole). The prescribed dose should appear in the table below (mark with a cirkle). The tablets should be taken 90 minutes before each treatment with radiotherapy. We kindly ask of you to fill in the point in time at which you take the tablets in the schedule below. The hospital staff also need to fill in some points in time in the schedule, so you are kindly asked to bring along the schedule to every treatment with radiation. Only take the tablets on days where radiotherapy is planned. You will be in daily contact with the staff at the hospital, if you shold have any concerns.

Height	m
Weight	kg
Body surface (m^2)	m^2

Body surface (m^2)	<1.6 m^2	1.6-1.9 m^2	>1.9 m^2
Dose nimorazole at 1st treatment	1.5 g (3 tabl)	2.0 g (4 tabl)	2.5 g (5 tabl)
Dose nimorazole at 2nd treatment	1 g (2 tabl)	1 g (2 tabl)	1 g (2 tabl)

Radio-therapy	Date	Number of tablets	The time you took the medicine (filled by patient)	Radiotherapy (time, filled by staff)	Remarks
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
33					
34					

NAME..... CPR.....

GUIDELINE IN THE ADMINISTRATION OF NIMORAZOLE TABLETS

From the clinic you have been handed out tablets as part of the treatment (Nimorazole). The prescribed dose should appear in the table below (mark with a cirkle). The tablets should be taken 90 minutes before each treatment with radiotherapy. We kindly ask of you to fill in the point in time at which you take the tablets in the schedule below. The hospital staff also need to fill in some points in time in the schedule, so you are kindly asked to bring along the schedule to every treatment with radiation. Only take the tablets on days where radiotherapy is planned. You will be in daily contact with the staff at the hospital, if you shold have any concerns.

Height	m
Weight	kg
Body surface (m^2)	m^2

Body surface (m^2)	<1.6 m^2	1.6-1.9 m^2	>1.9 m^2
Dose nimorazole at 1st treatment	1.5 g (3 tabl)	2.0 g (4 tabl)	2.5 g (5 tabl)
Dose nimorazole at 2nd treatment	1 g (2 tabl)	1 g (2 tabl)	1 g (2 tabl)

Radio-therapy	Date	Number of tablets	The time you took the medicine (filled by patient)	Radiotherapy (time, filled by staff)	Remarks
35					
36					
37					
38					
39					
40					
41					
42					
43					
44					
45					
46					
47					
48					
49					
50					
51					
52					
53					
54					
55					
56					