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## **Clarithromycin added to Bortezomib-Cyclophosphamide-Dexamethasone impairs health-related quality of life in multiple myeloma patients**

**Running title:** Clarithromycin and VCD impairs HRQoL

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## **Abstract**

**Objectives:** The Danish Myeloma Study Group initiated a randomized, placebo-controlled, double-blinded phase II study to investigate the efficacy of adding clarithromycin to cyclophosphamide-bortezomib-dexamethasone (VCD) induction therapy in transplant eligible, newly diagnosed multiple myeloma patients. The study was prematurely terminated due to severe complications, and no effect of adding clarithromycin was found. The aim of this study was to compare health-related quality of life (HRQoL) between the two groups and to explore the coherence hereof with adverse event (AE) registration by clinicians.

**Methods:** Patients completed three validated HRQoL questionnaires at inclusion, before cyclophosphamide priming, and two months after high-dose therapy (HDT). The mean score difference was interpreted by clinically relevant differences between groups. Spearman correlation analysis was used to compare patient-reported toxicities with AEs.

**Results:** Of 58 included patients, 55 participated in the HRQoL reporting. Before cyclophosphamide priming, patients in the clarithromycin group reported clinically relevant reduced HRQoL for eleven domains with persistent reduction in four domains two months after HDT. Poor correlation between patient-reported toxicities and clinician-reported AEs was observed.

**Conclusions:** Despite the premature study termination, our data demonstrate impaired HRQoL when clarithromycin was added to the VCD regimen. We found clear underreporting of toxicities by clinicians. ClinicalTrials.gov number NCT02573935

Key words: Multiple myeloma, Clinical trials, Quality of life, Transplantation

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## Introduction

Analyses of health-related quality of life (HRQoL) captured by patient-reported outcomes (PRO) are incorporated in most randomized phase II and III clinical cancer studies (1). Patient-experienced benefits and toxicities are valuable parameters for shared treatment decision-making in daily practice (2-4). Also, PRO data results are important from a regulatory perspective in the evaluation of medicinal products, which has been stated by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) when new drugs or drug combinations are approved (5, 6).

HRQoL during induction therapy and high-dose chemotherapy with stem cell support (HDT) in newly diagnosed multiple myeloma (MM) patients has been reported in more studies (7-11). In general, the patients report unchanged global quality of life (QoL) during induction therapy with clinically meaningful deterioration in global QoL, physical functioning, and increased degree of pain and fatigue two weeks after HDT. Two months after HDT the patients report full recovery and further improvement until 12 months after HDT (12).

The Danish Myeloma Study Group (DMSG) initiated a randomized, placebo-controlled double-blinded phase II study to investigate the efficacy and safety of adding clarithromycin to bortezomib-cyclophosphamide-dexamethason (VCD) induction therapy prior to HDT in newly diagnosed MM patients (13). Clarithromycin in combination with Lenalidomide and low-dose dexamethasone is been found to be an effective treatment regimen with manageable side effects in treatment naïve symptomatic MM patients (14). The rationale for this study, entitled the CLAIM study, was to test these previous findings using a randomized placebo-controlled study design with addition of patient-reported HRQoL captured by validated PRO questionnaires. In fact, a valid investigation of HRQoL during an anti-myeloma regimen with addition of clarithromycin has to our knowledge never been published.

The CLAIM study was prematurely terminated on 16 September 2016, after inclusion of 58 patients, due to a high incidence of serious adverse events (AE) in the intervention group. Response data did not suggest any effect of adding clarithromycin to the VCD regimen (13). The primary objective of this analysis was to evaluate the patient-reported HRQoL in patients receiving clarithromycin added to the VCD induction therapy. The secondary objective was to compare patient-reported toxicities to AEs reported by clinicians.

## **Patients and methods**

### ***Study design***

Study details have been published previously (13). Newly diagnosed transplant-eligible MM patients with treatment-demanding disease according to the International Myeloma Working Group criteria were eligible for inclusion (15). The patients were randomized (1:1 ratio) to treatment with clarithromycin 500 mg orally twice daily or a matching placebo tablet for 63 days in combination with VCD induction therapy. The VCD regimen consisted of three 21-day cycles of subcutaneous bortezomib 1.3 mg/square meter (sqm) day 1, 4, 8, 11, intravenous cyclophosphamide 500 mg per sqm on day 1 and 8, and 40 mg dexamethasone orally on day 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. After initiating the protocol an amendment was approved to include a fourth VCD cycle prior to stem cell harvest according to an update of the Danish National Multiple Myeloma guidelines. No changes were made in relation to dosage or duration of study medication or placebo with the amendment. The study was approved by the Danish Ethical Committee, the patients provided written informed consent before participation, and the trial was conducted in accordance with the principles of the Helsinki Declaration.

### ***Health-related quality of life assessment***

For HRQoL assessment, two “European Organisation for Research and Treatment of Cancer Quality of life” (EORTC) questionnaires were used; the cancer specific QoL instrument QLQ-C30 (16) and the Multiple Myeloma module QLQ-MY20 (17). The EORTC QLQ-C30 is a validated, reliable and the most commonly used instrument for HRQoL measurement in clinical trials with MM patients (12, 18). The QLQ-C30 contains one global QoL domain, five functional domains (physical, role, emotional, cognitive and social) and nine symptom domains (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) (19). The EORTC QLQ-MY20 contains two functional domains (future perspective and body image) and two symptom domains (disease symptoms and side effects of treatment). Each domain was scored from 0-100 and for the functional and global QoL domains, a higher score means better functioning/global QoL, and for the symptom domains, a higher score means a higher degree of symptoms.

For evaluation of peripheral neuropathy, the “Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity” (FACT/GOG- ntx) subscale was used, which is a single domain 11-item questionnaire (20). The questionnaire has been validated and used previously in myeloma patients for evaluation of treatment-related peripheral neuropathy (21, 22). The domain was scored from 0-44 and a higher score means a lower degree of peripheral neuropathy.

### ***Health-related quality of life data collection procedure***

The three questionnaires were scheduled to be completed by the patients at baseline (inclusion), before cyclophosphamide priming and two months after HDT. The patients were encouraged to complete the questionnaires electronically at home via a link sent by e-mail. The Internet-based tool of Electronic Data Capture platform has been well accepted by haematological patients (23). The email with a link was sent to patients at baseline, at day 60 and 180 after inclusion. If patients did not complete the questionnaire within 24 hours, a reminder was sent, and in case of non-response

seven days after the target date, the link to the questionnaire was blocked. Patients, who were not willing or able to answer the questionnaires electronically, completed the questionnaires by paper at study visits before cyclophosphamide priming and two months after HDT.

#### ***Adverse events reported by clinicians***

AEs were evaluated according to “Common Terminology Criteria of Adverse Events” (CTCAE) version 4.0 (24) at day 1 of each VCD induction cycle, at study visits before cyclophosphamide priming and two months after HDT by clinicians. All unresolved AEs at the visit before cyclophosphamide priming were followed by the responsible clinician until the AEs were resolved.

#### ***Statistical methods and handling of missing data***

Calculation of domain scores and handling of missing items were performed as described in EORTC and FACT scoring manuals (19, 25). For the analysis of the HRQoL mean scores results, mixed model for repeated measures with an unstructured covariance matrix was used. A baseline constrained model where baseline values are constrained to be equal across treatment groups was chosen (26). Due to early study termination sample size was lower than planned. Therefore the HRQoL results were primarily interpreted by thresholds of clinical relevance between treatment groups (27). A treatment group difference of  $\geq 5$  point was defined as clinically relevant for the EORTC domains and  $\geq 11.8$  points for the FACT/GOG-ntx subscale (28, 29).

To explore the impact of non-responses to scheduled questionnaires, sensitivity analyses of the results of the global QoL domain were performed using two methods (A and B). First, variables predicting non-responses were explored using odds ratio analyses (30-32). Variables tested for baseline non-responses were creatinine, hemoglobin, C-reactive protein and World Health Organization Performance Status (WHO PS) at baseline. For non-responses to the follow-up

questionnaires, grade 1-2 AE, grade 3-4 AE, postponed induction cycle (more than 42 days from day 1 cycle 1 to day 1 cycle 3), dose reduction of bortezomib, dexamethasone or cyclophosphamide, were tested as predictors for non-responses. In sensitivity analysis method A, multiple imputations were used. Missing scores were imputed using each patients' creatinine, hemoglobin, C-reactive protein, WHO PS, grade 3-4 AE, information on dose reduction of bortezomib, dexamethasone or cyclophosphamide, postponed induction cycle or other values of global QoL (33-35). In sensitivity analysis method B, we identified the non-responses in the dataset, which were timely coincident (7 days before to 30 days after) with the previously found predictive variables for non-responses. The timely coincident missing scores for the non-responses were replaced by the worst possible score for global QoL in the dataset, and the analysis was repeated.

Spearman correlation analysis was used to compare AEs assessed by clinicians with patient-reported toxicities. Cohen's criteria for medium effect size was used to calculate the minimal important difference (MID) for the clinically meaningful change (0.5 x standard deviation at baseline) and a score change above the MID was determined as clinical meaningful to the patient (36-38). We used Fleiss thresholds for agreement to interpret the rho score; rho values of <0.40 were poor agreement, values between 0.40 and 0.75 were moderate to good agreement, and values > 0.75 were excellent agreement (39).

P-values below 0.05 were considered significant. R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS institute, Cary, NC, USA). SAS was used for mixed model for repeated measures, whereas R package "mice" was used for multiple imputations.



## Results

### *Patient population and compliance*

From the time of inclusion of the first patient on 16 November 2015 until termination of the study on 16 September 2016, 58 patients were included. Three patients did not answer any of the questionnaires and were excluded from the HRQoL analysis. Of the patients included in the analysis, 25 patients were allocated to clarithromycin and 30 patients to placebo. Patient baseline characteristics are presented in Table 1.

The completeness rates of questionnaires were 84% in the clarithromycin group and 89 % in the placebo group. Mean scores at baseline and standard deviations for each domain and treatment group are presented in Table 2. The mean baseline scores in global QoL were imbalanced with a difference of 8.4 points between the two groups and a graph of change in global QoL score over time is presented in the supplementary appendix figure 1S. The number of patients in the study at baseline, before cyclophosphamide priming and two months after HDT and the number of completed questionnaires are presented in the CONSORT diagram in Figure 1. The main reason for early patient drop out was serious AEs, which was the case for four patients in the clarithromycin group and one patient in the placebo group.

Thirty-four patients (62%) completed the questionnaires electronically, and 21 patients (38%) chose paper questionnaires. Since some VCD induction cycles were postponed due to complications and some patients were treated with four cycles of VCD, not all patients completed the follow-up questionnaires at the scheduled time points before cyclophosphamide priming and two months after HDT. The follow-up questionnaires before cyclophosphamide priming were completed with a median of nine days too early (range -51 to 11) for the clarithromycin group and 12 days too early (range -41 to 1) for the placebo group. Also, the two months after HDT assessments were completed

with a median of four days too early (range -36 to 45) for the clarithromycin group and one day too early (range -38 to 19) for the placebo group.

### ***Comparison of HRQoL between treatment groups***

HRQoL domains with a clinical relevant difference in mean change of score before cyclophosphamide priming are presented in Figure 2 and the domains with no clinical relevant difference are presented in the supplementary appendix Figure 2S.

Before cyclophosphamide priming, the patients in the clarithromycin group reported clinically relevant reduced global QoL, physical, role, emotional and social functioning, body image and increasing fatigue, insomnia, disease symptoms, side effects of treatment, and peripheral neuropathy compared to the patients in the placebo group. Two months after HDT the clinical relevant reduced HRQoL was persistent for physical, role and social functioning, and insomnia. Only for diarrhea and constipation before cyclophosphamide priming and for constipation two months after HDT, the patients receiving clarithromycin reported clinically relevant reduced symptoms compared to the patients receiving placebo. The mean score difference for global QoL between the two groups was -16.2 points (95% CI -2.6;-29.8,  $p=0.021$ ) before cyclophosphamide priming and -4.9 (95% CI -11.1; 20.8,  $p=0.54$ ) two months after HDT. The p-values for comparison of mean change in score from baseline between the two treatment groups are presented in the supplementary appendix Table 1S.

The only statistical significant predictor for non-responses to scheduled questionnaires was registration of grade 3 or 4 AEs with an odds ratio of 4.2 ( $p=0.03$ ) before cyclophosphamide priming and 3.5 ( $p=0.04$ ) two months after HDT. A table of grade 3 or 4 AEs is presented in the supplementary appendix, table 2S. Using multiple imputation for non-responses coincident with registration of grade 3 and 4 AEs (method A), the mean score differences for global QoL were -15.8

(95% CI -29.1; -2.6 p=0.019) before cyclophosphamide priming and -3.1 (95% CI -17.9; 11.7, p=0.68) two months after HDT. For method B we replaced the score of non-responses with the worst possible reported score for global QoL in the dataset, which was zero. We found mean score differences of -20.4 (95% -35.5; -5.3, p=0.009) before cyclophosphamide priming and -6.4 (95% -22.6; 9.7, p=0.009) two months after HDT. The results of and the sensitivity analyses method A and B are illustrated in figure 3.

#### ***Adverse events registered by clinicians and patient-reported toxicities***

In the correlation analysis we compared clinician registered AEs to the patient-reported toxicities for the eight toxicity domains of fatigue, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and peripheral neuropathy. Since some discrepancies were observed between the time points of AE evaluation by clinicians at the study visits and the time points of answered questionnaires, time effect correlation analyses were carried out. For constipation we observed a statistically significant time effect before cyclophosphamide priming ( $\rho = -0.39$ ;  $p = 0.012$ ) and two months after HDT ( $\rho = 0.47$ ;  $p = 0.005$ ). Also, for diarrhoea, there was a statistically significant time effect two months after HDT ( $\rho = -0.34$ ;  $p = 0.045$ ). Therefore, correlation analyses were not performed for constipation at the two follow-up time points and for diarrhoea two months after HDT. Overall, poor correlations between the patient-reported toxicity and clinician registered AEs for all six toxicities were found with  $\rho$  values less than 0.4 (Table 3).

#### **Discussion**

Our data demonstrate that MM patients report a clinically relevant reduced HRQoL, when clarithromycin is added to the VCD regimen with persisting HRQoL sequelae two months after HDT. Using registered toxicities by CTCAE this knowledge could not be concluded from the clinicians' AE evaluation, since they underreported symptomatic toxicities.

A limitation of our results is that it is based on an underpowered study due to premature study termination with a poor questionnaire completion rate, which made us unable to obtain a valid statistical result. Still, when comparing our results to existing literature of HRQoL during induction therapy and HDT in MM patients, it is noteworthy that the patients in the clarithromycin group reported decreased HRQoL after induction phase (40, 41). Our findings could be explained by the pharmacokinetics of bortezomib and clarithromycin. Bortezomib is primarily metabolized by the cytochrome P450 enzyme CYP3A4, which is known to be inhibited by clarithromycin. Thus, the reduced HRQoL could be a result of increased biological effect of bortezomib in the clarithromycin group (13). Clarithromycin has been used in other treatment regimens for MM often in combination with Lenalidomide and low-dose dexamethasone, which is found to have favorable toxicity profile (14). This discrepancy in AE findings compared to our study supports the explanation of being caused by the pharmacokinetic interaction between bortezomib and clarithromycin, when those two drugs are administered in parallel. In the CLAIM study, special precaution was made for the potential risk of QT prolongation, ventricular tachycardia and sudden death caused by clarithromycin. Severe cardiac disease or QT prolongation was exclusion criteria and ECG was performed at screening, on day 4 and before start of VCD cycle 2. If the patient developed QT prolongation (QTc interval > 500 msec) the clarithromycin/placebo treatment was permanently discontinued. However, no serious cardiovascular events were reported during the study (13).

In clinical studies, AEs are traditionally collected as described in CTCAE guideline by clinicians (24). Drug efficacy and toxicity profile analyses are included in the process where a given drug is considered for approval by the FDA and EMA. In earlier studies comparison of CTCAE and patient-reported toxicities revealed underreporting of toxicities by the clinicians as compared with patient-reported toxicities (42, 43). Our study confirmed this discrepancy, thereby emphasizing the importance of including HRQoL as an endpoint in clinical trials. Also, it highlights the potentially important role of integrating PRO data in real-time safety monitoring in clinical trials as well as in the

daily clinical practice (44). A limitation in the interpretation of our results when comparing patient-reported toxicities and clinician reported AEs is the lack of synchronous registration of toxicities by clinicians and patients and the retrospective nature of the analysis. Still, we believe the results are convincing since clinicians may tend to underreport AEs (42).

In this current study, we observed that there were non-responses to scheduled questionnaires, which is a common challenge in PRO data collection, analysis and interpretation (32, 45, 46). The potential consequences of non-responses are decreased precision and power, and more seriously, the introduction of bias to the PRO data results, when a patient fails to complete a questionnaire because of severe illness or other reasons. It is recommended to design clinical studies with PRO data collection with focus on minimization of non-responses and to perform sensitivity analysis to explore the impact of non-responses on the PRO data results (46, 47). In our study, more patients in the clarithromycin group dropped out early due to serious AEs resulting in a lower questionnaire completion compared to patients in the placebo group. Therefore, the analyses performed are hypothetically fragile for biased results. We performed analyses to explore the impact of non-responses of being “missing not at random” (48). We examined the mechanisms of non-responses and found that registration of a grade 3-4 AEs was a predictor of non-responses, which confirms that some of the non-responses were “missing not at random”. When integrating this information into the sensitivity analysis method B it was confirmed that non-responses to questionnaires do impact the results of the global QoL domain and that our results might be conservative. However, in the sensitivity analysis method A using multiple imputations, we found no impact of non-responses on the global QoL results. Limitations in using the multiple imputation method in our study are the low sample size and a limited number of patients with grade 3 or 4 AEs reporting a global QoL score. Also, the global QoL domain is described as a “distal” measure with limitations in interpretability due to greater mediation by personal and environmental characteristics rather than disease and treatment related changes (49).

In conclusion, the CLAIM study demonstrated that adding clarithromycin to the VCD regimen in MM patients resulted in impaired HRQoL during the VCD induction phase continuing up to two months after HDT. The study emphasizes that well-designed randomized, double-blinded and placebo-controlled studies with PRO data collection is necessary to determine drug risk benefit assessment, and also to test well-known drugs in new combinations. Treatment with clarithromycin and VCD in parallel cannot be recommended because of a higher risk of complications and reduced HRQoL. The PRO data in the CLAIM study played a key role in explaining the causality link between the observed complications and the possible interaction between clarithromycin and bortezomib. In addition, the study demonstrates that “real-time” monitoring of patient-reported toxicities as a supplement to CTCAE registration should be included in clinical trials. The National Cancer Institute’s PRO version of the common terminology criteria for adverse events (PRO-CTCAE) has been validated and found feasible in clinical trials for documentation of symptomatic toxicities (50). With this tool, PRO data can be incorporated into future clinical cancer studies. Moreover, PRO data will most likely be a useful tool in shared treatment decision making in clinical practice. Studies designed to validate the use of PRO data in daily practice are warranted.

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**Table 1.** Patient demographics

Characteristics	Clarithromycin group N=25	Placebo group N=30
Median age, years (IQR) [range]	64 (55; 67)[40; 70]	62 (55; 66)[37; 70]
Sex, Male (N)	19 (63.3%)	19 (76.0%)
Type of myeloma (N)		
IgA	3 (12.0%)	9 (30.0%)
IgG	18 (72.0%)	16 (53.3%)
Light chain	4 (16.0%)	5 (16.7%)
Disease stage according to ISS (N)		
I	7 (29.2%)	7 (24.1%)
II	9 (37.5%)	18 (62.1%)
III	8 (33.3%)	4 (12.9%)
Missing	1	1
B-2 microglobulin, mg/l (SD)[range]	3.4 (2.4;7.2)[1.6;27.1]	3.6 (2.6;4.6)[1.9;23.4]
Missing values	1	1
LDH, units/l (SD)[range]	164 (146;212)[101;267]	178 (158;215)[110;487]
Missing values	1	3
Serum creatinine, $\mu$ mol/l (SD)[range]	81 (69;92)[50;271]	84 (67;97)[45;167]
WHO performance status scale (N)		
0	13 (52.0%)	17 (56.7%)
$\geq 1$	12 (48.0%)	13 (43.3%)

IQR; Interquartile range, ISS; International Staging System, LDH; Lactate dehydrogenase, WHO; World Health Organization

**Table 2.** Baseline mean scores and standard deviations for the two treatment groups

<b>Health-related quality of life domains</b>	<b>Clarithromycin group</b> Mean score (SD) N=25	<b>Placebo group</b> Mean score (SD) N=30
<b>EORTC QLQ-C30</b>		
Global QoL	51.7 (25.3)	60.1 (28.0)
Physical Functioning	64.6 (26.5)	63.9 (30.9)
Role Functioning	48.6 (35.8)	48.3 (41.9)
Emotional Functioning	75.7 (17.9)	72.3 (21.2)
Cognitive Functioning	86.8 (17.0)	81.0 (19.1)
Social Functioning	78.5 (25.8)	75.0 (35.3)
Fatigue	39.4 (30.0)	39.5 (29.0)
Nausea and vomiting	9.0 (12.0)	9.2 (17.0)
Pain	45.8 (39.7)	55.7 (40.2)
Dyspnoe	16.7 (19.7)	13.8 (24.4)
Insomnia	27.8 (27.2)	39.1 (30.9)
Appetite loss	13.9 (25.9)	16.1 (30.4)
Constipation	34.7 (37.4)	28.6 (32.3)
Diarrhoea	8.3 (17.7)	4.8 (11.9)
Financial difficulties	5.8 (12.9)	7.1 (18.9)
<b>EORTC QLQ-MY20</b>		
Disease symptoms	32.1 (21.2)	39.8 (30.4)
Side effects of treatment	13.6 (9.9)	13.4 (13.4)
Future Perspective	76.8 (34.0)	84.0 (26.7)
Body image	41.5 (29.1)	41.2 (38.4)
<b>FACT/GOG-Ntx subscale</b>	<b>8.7 (9.3)</b>	<b>8.0 (8.6)</b>

EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire, EORTC QLQ-MY20; European Organisation for Research and Treatment of Cancer Multiple Myeloma module, FACT/GOG-Ntx subscale; Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity subscale, SD; Standard deviation

**Table 3.** Correlation between registered adverse events by clinicians and patient-reported toxicities

Patient-reported toxicities	Before cyclophosphamide priming		Two months after HDT	
	Correlation		Correlation	
	Rho	P-value	Rho	P-value
Diarrhoea	-0.10	0.53	NA	NA
Constipation	NA	NA	NA	NA
Nausea and vomiting	-0.11	0.51	-0.31	0.06
Fatigue	0.35	0.023	-0.01	0.97
Insomnia	0.20	0.20	-0.09	0.61
Peripheral neuropathy	0.29	0.075	-0.02	0.90
Dyspnoea <sup>2</sup>	-	-	-	-
Appetite loss	0.02	0.92	0.26	0.13

<sup>1</sup>Any grade of toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, patient-reported change from baseline above the threshold for minimal important difference calculated by Cohens' medium effect size (0.5x standard deviation of mean baseline score) for the domain, <sup>2</sup>Correlation calculation was not possible, since none of the patients had dyspnoea registered as an adverse event, NA; correlation analysis was not performed since a statistically significant time effect was found.

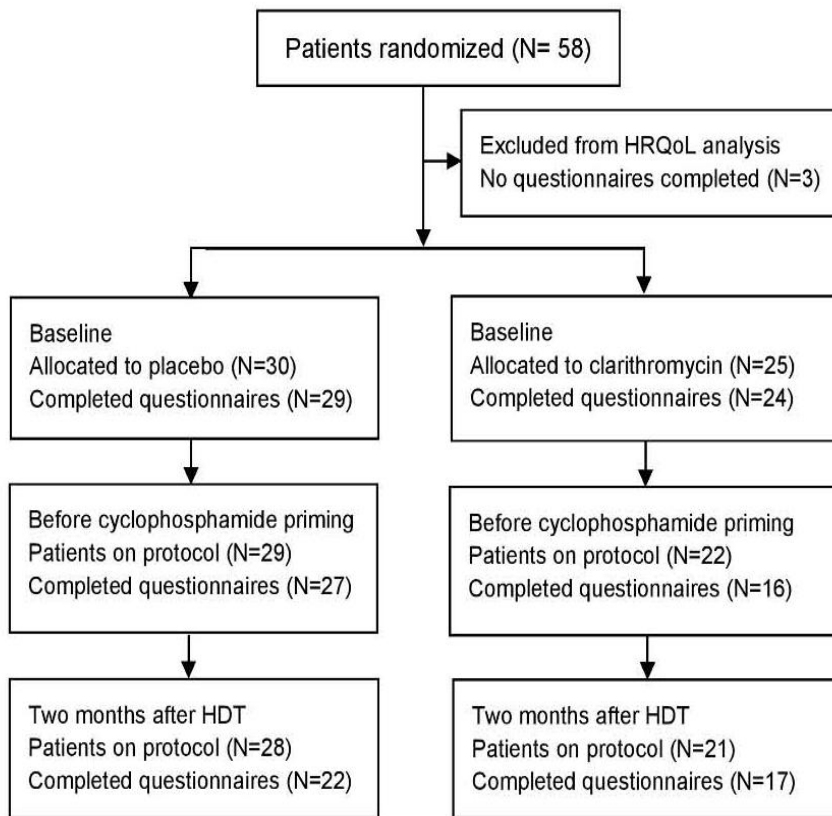
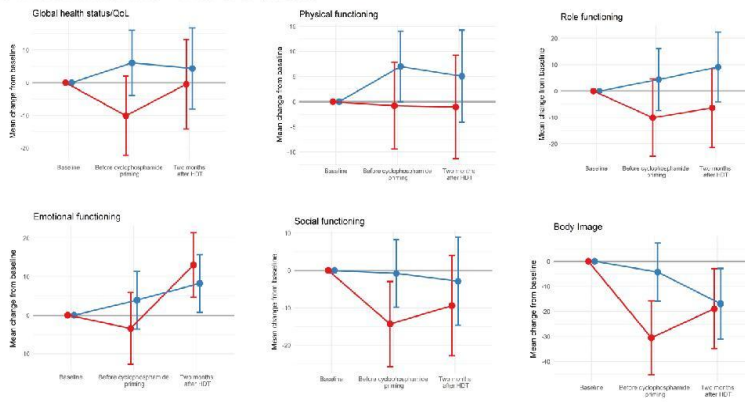
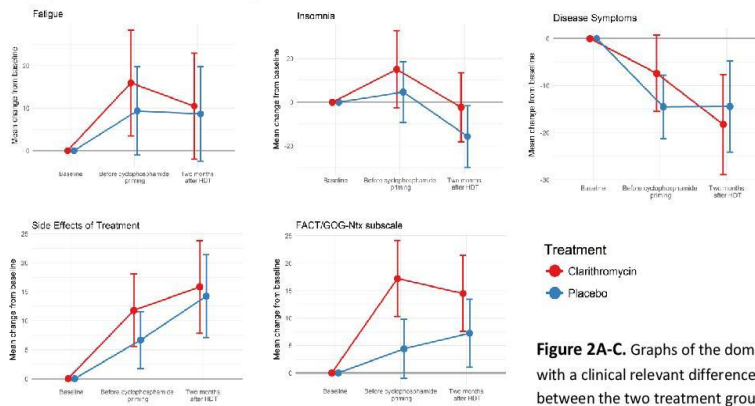


Figure 1. CONSORT flow diagram of the number of patients in follow-up and number of completed questionnaires.

**A. Functional domains – in favor of placebo**



**B. Symptom domains – in favor of placebo**

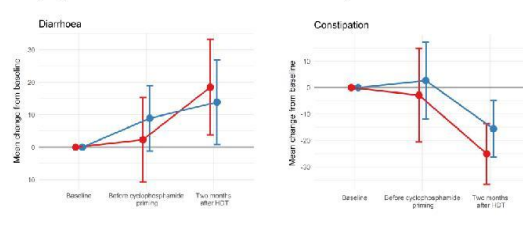


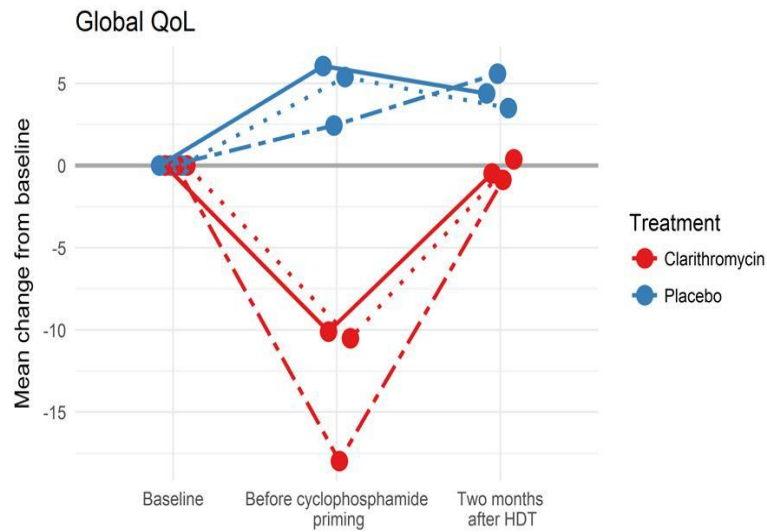
**Treatment**  
● Clarithromycin  
● Placebo

**Figure 2A-C.** Graphs of the domains with a clinical relevant difference between the two treatment groups before cyclophosphamide priming. For physical, role and social functioning and insomnia and constipation the clinical relevant differences were persistent two months after HDT.

For the functional domains including global health status/QoL, a higher score means better functioning/QoL, and for the symptom domains, a higher score means a higher degree of symptoms.

**C. Symptom domains – in favor of clarithromycin**





**Figure 3.** Impact of non-responses to scheduled questionnaires. The analysis using mixed model repeated measure (solid lines), sensitivity analysis method A using multiple imputations (dotted lines) and sensitivity analysis methods B using missing score replacement with zero (spotted lines).