# Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma

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## ABSTRACT

In the prospective phase 3 HOVON-50/GMMG-HD3 trial, patients randomized to TAD (thalidomide, doxorubicin, dexamethasone) had a significantly higher response rate (at least PR) after induction compared with patients randomized to VAD (vincristine, adriamycin, dexamethasone, 72% *vs.* 54%, $p<0.001$). Complete remission (CR) and very good partial remission (VGPR) were also higher after TAD. After High Dose melphalan 200mg/m$^2$ response was comparable in both arms, 76% and 79% respectively. However, CR plus VGPR were significantly higher in the patients randomized to TAD (49% *vs.* 32%, $p<0.001$). CTC grade 3-4 adverse events were similar in both arms.

Key words: thalidomide, untreated multiple myeloma

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## Introduction

Induction therapy, such as the combination of vincristine, doxorubicin and dexamethasone (VAD), followed by stem cell collection and autologous stem cell transplantation is currently considered the standard treatment for younger myeloma patients.[1,2,3] Recently thalidomide-based regimens have been shown to be highly effective as first line treatment in terms of response and event free survival. New induction schedules like the thalidomide-dexamethasone combination are advocated as preparation regimens, with the rationale that these increase the initial response rate which may result in a higher (complete) response rate and prolonged survival following high-dose therapy and autologous stem cell transplantation.[4-8] However, others have questioned the value of VAD as initial therapy in multiple myeloma (MM) and have emphasized the care needed before drawing conclusions from surrogate outcomes such as response rate.[9] The objective of the HOVON 50 MM/GMMG-HD3 phase 3 trial was to evaluate the efficacy of thalidomide combined with intensive therapy in previously untreated patients.[10]

## Design and Methods

Patients with newly diagnosed MM, Salmon and Durie stage II or III, age 18-65 years, were eligible for inclusion in the HOVON-50/GMMG-HD3 study. Informed consent was obtained prior to randomization. According to the Declaration of Helsinki, the protocol was approved by the Research Ethics Board of each participating hospital. Patients were randomly assigned to arm A: 3 cycles of VAD: vincristine (0.4 mg, IV rapid infusion on days 1-4), doxorubicin (9 mg/m$^2$, IV rapid infusion on days 1-4) and dexamethasone 40

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mg orally (days 1-4, 9-12, 17-20)[11] or to arm B, the same regimen but with thalidomide 200 - 400 mg orally, days 1-28 instead of vincristine (TAD). Cycle 2 started at day 29, cycle 3 at day 57. Thalidomide was started at day 1 of the first TAD cycle and was stopped 2 weeks before stem cell mobilization was started. The thalidomide dose could be escalated to a maximum 400 mg when tolerability was good. Patients in arm B received thrombosis prophylaxis consisting of subcutaneously low molecular weight heparin (LMWH) nadroparine 2,850 IE anti-Xa or 5,700 anti-Xa when weight >90 kg.[12] Stem cells were mobilized using the CAD regimen, i.e. cyclophosphamide 1000 mg/m$^2$ iv day 1, doxorubicin 15 mg/m$^2$, iv rapid infusion on days 1-4, dexamethasone 40 mg orally on days 1-4, given at 4-6 weeks after induction treatment, plus G-CSF 5 mg/kg twice daily until collection. After induction therapy, all patients were to receive 1 or 2 courses of high dose Melphalan (HDM) 200 mg/m$^2$ with autologous stem cell rescue. Centers committed to single or double HDM before start of study. Patients randomized to arm A received maintenance therapy with α-interferon (3×10$^6$ IU, three times week) and patients randomized to arm B received Thalidomide 50 mg daily without venous thromboembolism (VTE) prophylaxis. Response was evaluated as intention to treat according to the EBMT criteria and required a negative immune fixation for patients in CR.[14] Recently, achievement of a VGPR, defined as a 90% or greater reduction in the serum M-protein plus urinary M-protein level < 100 mg/24 hours has been recognized. This criterion was, therefore, also included in the response evaluation.[15] Response was evaluated after induction treatment and at least 3 months after HDM 1.

**Table 1.** Patient characteristics.

| | *Arm A: VAD* | *Arm B: TAD* | *Total* |
|---|---|---|---|
| Total | 201 | 201 | 402 |
| Sex | | | |
| male | 115 | 133 | 248 |
| female | 86 | 68 | 154 |
| Age | | | |
| median | 56 | 57 | 56 |
| range | 36-65 | 34-65 | 34-65 |
| M-protein | | | |
| IgA | 47 | 38 | 85 |
| IgG | 108 | 127 | 235 |
| IgM | 1 | 1 | 2 |
| IgD | 1 | 3 | 4 |
| LCD | 42 | 30 | 72 |
| unknown | 2 | 2 | 4 |
| Serum β-2M | | | |
| Median mg/L | 3.1 | 3.6 | 3.3 |
| range | 0.1 - 34.8 | 0.5 – 53.6 | 0.1 - 53.6 |
| number | 172 | 172 | 344 |
| Albumin g/L | | | |
| median | 36.0 | 3542 | 36 |
| range | 20-53.0 | 4.2-57.4 | 4.2-57.4 |
| number | 182 | 181 | 363 |
| Stage S and D | | | |
| IIA | 37 | 33 | 70 |
| IIB | 1 | 1 | 2 |
| IIIA | 134 | 139 | 273 |
| IIIB | 28 | 26 | 54 |
| unknown | 1 | 2 | 3 |
| ISS | | | |
| I | 87 | 75 | 162 |
| II | 37 | 43 | 80 |
| III | 33 | 45 | 78 |
| unknown | 44 | 38 | 82 |

*S and D: Salmon and Durie; LCD: light chain disease; ISS: International Staging System.*

## Results and Discussion

A first interim analysis was performed on 402 patients of the 1,240 included in the trial, 201 patients per treatment arm with validated data, registered before August 2004. Median age was 56 years (range 34-65), 248 male and 154 female patients. Most patients (81%) had stage III myeloma according to Salmon and Durie. According to the International Staging System (ISS) 163 patients were in stage I, 81 in stage II and 78 in stage III, while 80 patients could not be classified due to missing β2-microglobulin and/or albumin data.[13] Patient characteristics were in general equally distributed between both arms (Table 1).

The total response (≥ PR) after 3 courses of TAD was significantly higher compared with the response after 3 courses of VAD (72% *vs.* 54%, $p$<0.001). In addition, VGPR plus CR was higher in patients receiving TAD (arm B, 33% CR 4%) *vs.* VAD (arm A, 15%; CR 2%, $p$<0.001). Total response rates (PR, VGPR plus CR) following HDM1 were comparable in both arms: VAD +HDM1; 76%, TAD plus HDM1; 79% ($p$=0.55). However, TAD followed by HDM1 resulted in a significantly higher proportion of patients achieving VGPR plus CR, 49% *vs.* 32% ($p$<0.001), while the CR percentages were not statistically different (16% *vs.* 11%, $p$=0.19). The ISS had no impact on response rate, nor was there an association between ISS and treatment arm. Thalidomide could be given at full dose to 62% of patients, was reduced in 17% of patients, had to be stopped in 19% of patients, while no data were available for 2% of patients. CTC grade 3-4 events were recorded in 33% of patients during VAD and in 41% of patients during TAD ($p$=0.13). Grade 3-4 neurology occurred in 7% of patients during VAD and in 12% of patients during TAD ($p$=0.09). All grade 3-4 adverse events during induction therapy are listed in Table 2. Twenty seven patients (13%) in arm A and 37 patients (18%) in arm B went off protocol treatment without receiving HDM, mainly due to excessive toxicity (3%), intercurrent death (6%) or progressive disease (5%) comparable in both arms. The incidence of VTE during induction therapy was published previously.[12] In short:

**Table 2.** Number (%) of patients with adverse events CTC grade 3-4 during VAD/TAD cycles 1-3.

| | *Arm A: VAD (n=199 )** | | *Arm B: TAD (n=200)** | | *p value* |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Any adverse event | 66 | 33 | 81 | 41 | 0.13 |
| Allergy/immunology | – | – | 1 | 1 | 1.00 |
| Auditory/hearing | – | – | 1 | 1 | 1.00 |
| Cardiovascular arrythmi | 3 | 2 | 3 | 2 | 1.00 |
| Cardiovascular. function | 15 | 8 | 17 | 9 | 0.72 |
| Coagulation | 4 | 2 | 7 | 4 | 0 .54 |
| Constitutional symptoms | 10 | 5 | 14 | 7 | 0.41 |
| Dermatology/skin | 3 | 2 | 2 | 1 | 0 .69 |
| Endocrine | 3 | 2 | 4 | 2 | 1.00 |
| GI | 10 | 5 | 16 | 8 | 0.23 |
| Hemorrhage | 1 | 1 | 3 | 2 | 0.62 |
| Hepatic | 7 | 4 | 6 | 3 | 0 .77 |
| Lymphatic | 1 | 1 | – | – | 0.50 |
| Metabolic | 17 | 9 | 10 | 5 | 0.16 |
| Musculoskeletal | 2 | 1 | 2 | 1 | 1.00 |
| Neurology | 14 | 7 | 24 | 12 | 0 .09 |
| Ocular | – | – | 1 | 1 | 1.00 |
| Pain | 9 | 5 | 9 | 5 | 0.99 |
| Pulmonary | 7 | 4 | 7 | 4 | 0.99 |
| GU and renal | 1 | 1 | 3 | 2 | 0 .62 |
| Other | 1 | 1 | 1 | 1 | 1.00 |

** Adverse events data were not available in 3 patients (2 in arm A, 1 in arm B). There were some (expected) events, that didn't have to be reported as adverse events (diarrhea, mucositis).*

VTE incidence in both arms was reported to be comparable (Arm A, 4% and Arm B, 8%, $p$=0.08).

Impressive response rates have been reported for first line therapies that combine the conventional anti-myeloma drugs with novel agents such as thalidomide, lenalidomide or bortezomib.[16-18] Our study shows that more effective induction therapy by including thalidomide not only improves the remission status after induction but that the superior response is maintained until after intensification. It is remarkable that this better response was only reflected by a higher percentage of VGPR while total response and CR rate were not improved. Do these results further support the value of VAD as initial therapy in multiple myeloma? One would think so, although the better quality of the response induced by thalidomide must be balanced against the greater toxicity and the need for VTE prophylaxis associated with the combination. It is not yet known whether these increased response rates are translated in prolonged EFS and OS. Recently published studies showed that only thalidomide maintenance following autologous transplantation prolonged event-free survival (EFS) and overall survival (OS) while thalidomide given during all phases of treatment (induction, intensification and maintenance), only prolonged EFS but not OS, due to multi-drug resistant relapses after transplantation.[19,20]

We conclude that thalidomide as part of initial treatment improves pre- and post-transplant response by increasing the percentages of patients achieving a VGPR. Longer follow-up is needed to establish the effect on long term outcome. Our study supports the exploration of other combinations with novel agents that may induce even higher response rates and are probably associated with fewer side effects. Promising schemes in this respect are bortezomib, dexamethasone, with or without doxorubicin (PAD) and lenalidomide combined with dexamethasone.[16-18]

## Authorship and Disclosures

HML, PS, HG: principal investigators, substantial contribution to design, analysis and interpretation of the data, drafting or revising the article for intellectual content, final approval of manuscript; UB, BvdH, JS, RB, IB, GB, ISW, AC, SZ, HM, PJ, CS, MvMK, HS, MHvO, MS, RN, HS, WB, GV, OdW, PW, SW, UD, EV substantial contribution to design, analysis and interpretation of the data, drafting or revising the article for intellectual content, final approval of manuscript. The authors reported no potential conflicts of interest.

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