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## Original Paper

# Recombinant Human Granulocyte–Macrophage Colony-stimulating Factor After Combined Chemotherapy in High-grade Non-Hodgkin's Lymphoma—a Randomised Pilot Study

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**High-grade non-Hodgkin's lymphomas (NHL) can potentially be cured with combination chemotherapy, although the optimum schedules still have to be defined. Clinical trials with intensive chemotherapy are predominantly limited by myelosuppression. Here, haematopoetic growth factors open up the possibility of reducing chemotherapy-associated toxicities. In this randomised pilot study, we investigated the effects of a recombinant human granulocyte–macrophage colony-stimulating factor (rhGM-CSF) following combined chemotherapy with vincristine, doxorubicin, cyclophosphamide, prednisone and etoposide (VACPE). A total of 35 patients with high-grade NHLs were randomised to receive either rhGM-CSF or placebo during the first two chemotherapy cycles and rhGM-CSF for all following cycles. rhGM-CSF was administered at a dosage of 5 μg/kg for 10 days or until neutrophils were >1/nl following chemotherapy. The analyses revealed a significant reduction of neutropenia and duration of neutropenia in the rhGM-CSF group. Adverse events were rare and generally mild apart from one anaphylactoid reaction. No effects of rhGM-CSF were observed concerning the platelet nadir or duration of thrombocytopenia. The benefit of rhGM-CSF for response induction and survival via rhGM-CSF-supported dose intensification remains to be determined.**

**Key words: high-grade non-Hodgkin's lymphoma, GM-CSF, chemotherapy**
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## INTRODUCTION

HIGH-GRADE NON-HODGKIN'S LYMPHOMAS (NHLs) can potentially be cured with combination chemotherapy [1]. A number of clinical trials have been undertaken to improve the clinical results. Although second- and third-line regimens showed encouraging data in phase two studies, there is still no evidence for an improved outcome of high-grade NHLs in comparison with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) according to recently published phase III trials [1–13]. Whether there is a chance to improve the clinical results by intensification of chemotherapy regimens including autologous bone marrow transplantation (ABMT) or peripheral stem cell transplantation (PSCT) following myeloablative therapy is still a matter for discussion [1, 6, 14–19]. Even randomised trials comparing standard chemotherapy with early ABMT or PSCT have not shown any advantage so far [17–21]. Additionally, high-dose chemotherapy has been limited by severe aplasia and its attendant toxicities such as high infectious morbidity and severe bleeding [1].

Recombinant haematopoetic growth factors (CSF) have been shown to shorten the length of myeloid aplasia and thus become important adjuncts in high-dose chemotherapy approaches, because these factors may increase the safety of intensive chemotherapeuty regimens [20–26]. Additionally, CSFs may support dose escalation studies that offer hope for complete remissions and disease-free survival (DFS). One of these factors is the recombinant human granulocyte–macrophage colony-stimulating factor (rhGM-CSF), a regulatory glycoprotein that promotes the proliferation and differentiation of myeloid progenitor cells in intermediate stages and, under certain circumstances, erythroid and megakaryocytic colonies *in vitro*. It also enhances the function of mature neutrophils and monocytes [20, 22]. In recent studies of patients with lymphomas, those patients who received rhGM-CSF had a shortened duration of severe neutropenia and hospitalisation when compared to patients who received placebo [27, 28].

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In the present study, we investigated the effects of rhGM-CSF in a prospective double-blind randomised pilot trial in high-grade NHLs using intensified chemotherapy consisting of vincristine, doxorubicin, cyclophosphomide, prednisone and etoposide (VACPE) [29].

## PATIENTS AND METHODS

*Patients*

A total of 35 patients with high-grade NHLs were entered into the study and randomised to receive either rhGM-CSF or placebo. To be eligible for chemotherapy, patients had to be in stage II–IV or stage I with extranodal involvement or bulky disease (>5 cm). Consecutive patients with high-grade NHLs were entered. Informed consent according to the criteria of the local ethics committee was required for participation.

All patients but 1 were evaluable for response and toxicity. This 1 patient was not treated according to the protocol. The diagnosis of high-grade NHL was based on morphological and immunohistochemical examination of biopsies from involved lymph nodes, bone marrow or liver. High-grade lymphomas were classified according to the Kiel classification [30]. 18 patients showed a centroblastic NHL, 3 an immunoblastic NHL, 4 a large cell anaplastic (Ki1) lymphoma, 7 a T-cell lymphoma and 2 had other high-grade lymphomas (Table 1). 3 patients were assigned stage $I_{E,bulky}$, 13 stage II, 3 stage III and 15 stage IV according to Ann Arbor classification [31] (Table 1).

*Table 1. Patients' characteristics*

| | Group A (GM-CSF) | Group B (placebo*) | Total |
|---|---|---|---|
| Patients, eligible | 17 | 18 | 35 |
| Patients, evaluable | 17 | 17 | 34 |
| Age, years (range) | 55 (37–74) | 50 (16–69) | (16–74) |
| Male/female | 8/9 | 9/8 | 17/17 |
| Histological subtype | | | |
| Centroblastic | 12 | 6 | 18 |
| Immunoblastic | 2 | 1 | 3 |
| Lymphoblastic | | 1 | 1 |
| Ki-1 lymphoma | 1 | 3 | 4 |
| Pleomorphic T-cell | 2 | 3 | 5 |
| PTCL | | 1 | 1 |
| AILD | | 1 | 1 |
| Unclassified B-cell | | 1 | 1 |
| Stage | | | |
| I | 1 | 2 | 3 (9%) |
| II | 7 | 6 | 13 (38%) |
| III | 1 | 2 | 3 (9%) |
| IV | 8 | 7 | 15 (44%) |
| A (without symptoms) | 9 | 6 | 15 (44%) |
| B (with symptoms) | 8 | 11 | 19 (56%) |
| Performance status | | | |
| >70% | 6 | 8 | 14 (41%) |
| ≤70% | 11 | 9 | 20 (59%) |
| LDH | | | |
| ≤200 U/ml | 4 | 9 | 13 (38%) |
| >200 U/ml | 13 | 8 | 21 (62%) |
| Extranodal sites | | | |
| <2 | 11 | 9 | 20 (59%) |
| ≥2 | 6 | 8 | 14 (41%) |

*Placebo in cycles one and two, rhGM-CSF in cycles three to five (six). PTCL, peripheral T-cell lymphoma; AILD, angioimmunoblastic lymphoma; LDH, lactate dehydrogenase.

19/34 (56%) patients were symptomatic and 21/34 (62%) patients had one or more risk factors according to Shipp [32] as a performance status <70%, an elevated lactate dehydrogenase (LDH) serum level and more than two extranodal manifestations of the lymphoma.

*Study design*

The pretreatment evaluation included physical examination, complete blood cell count (CBC), differential white cell count, serum levels of immunoglobulins, serum chemistry screen, bone marrow histology and cytology, abdominal ultrasonography, X-ray of the chest, computed tomography (CT) scan of the tumour regions, facultative gastroscopy and biopsies. Follow-up assessments included weekly CBC and serum chemistry profiles before each treatment. Other diagnostic procedures initially demonstrating presence of the disease (such as CT scans, ultrasonic investigations, X-ray or bone marrow biopsies) were repeated every two to three courses.

Tumour response was evaluated according to the definitions of the World Health Organization (WHO) as complete remission (CR), partial remission (PR), no change (NC) and progressive disease (PD). Further analyses included granulocyte and platelet nadir, duration of cytopenia, days of fever >38°C and days requiring systemic antibiotic therapy. Early death was defined as death during the first 6 weeks of treatment.

The patients received a combination chemotherapy consisting of 2 mg vincristine (V) day 1 intravenously (i.v.), 25 mg/m$^2$ doxorubicin (A) days 1–3 i.v., 800 mg/m$^2$ cyclophosphamide (C) day 1 as a 30-min infusion, 60 mg/m$^2$ prednisone (P) days 1–7 orally (p.o.) and 120 mg/m$^2$ etoposide (E) days 1–3 as a 1-h infusion. This cycle (VACPE) was repeated on day 22 for up to five cycles in stages I–III and six cycles in stage IV. The patients were prospectively randomised in a double-blind trial for the first two cycles to receive either 5 μg/kg rhGM-CSF subcutaneously (Essex Pharma GmbH, Munich, Germany; Schering Plough, Kenilworth, New Jersey, U.S.A.) (group A) or placebo (group B) beginning on day 4 of each cycle until peripheral recovery (granulocytes >1000/μl). The rhGM-CSF is produced in *Escherichia coli* and used in its unglycosylated protein with a molecular weight of 14477 daltons [33, 34]. All patients received rhGM-CSF for cycles three to five [6]. In patients with stage I–III, a consolidation radiotherapy with 36 Gy extended field and a 10 Gy boost to the involved regions was administered.

*Statistics*

The Wilcoxon–Mann–Whitney U-test and $\chi^2$ test were used to determine the significance of differences between peripheral blood counts.

## RESULTS

In total, 35 patients with high-grade NHLs were eligible for this randomised pilot study and 34 patients were evaluable for response and rhGM-CSF effects. Between the randomised groups, there were no significant differences concerning age, sex and risk factors according to Shipp [32]. With respect to histological subtypes, there was a slight preponderance of T-cell lymphomas in group B (Table 1). The overall response was 33/34 (97%) patients with a CR rate of 79% (Table 2), with no significant difference between patient groups. So far, there are no significant differences in DFS and overall survival between the groups (median follow-up 22 months).

Concerning the effect of rhGM-CSF, there was no significant

*Table 2. Response to chemotherapy (VACPE)*

| Response | Group A (GM-CSF) | Group B (placebo*) | Total |
|---|---|---|---|
| CR | 14/17 (82%) | 13/17 (76%) | 27/34 (79%) |
| PR | 3/17 (18%) | 3/17 (18%) | 6/34 (18%) |
| CR+PR | 17/17 (100%) | 16/17 (94%) | 33/34 (97%) |
| NR | 0 | 1/17 (6%) | 1/34 (3%) |
| Median DFS† (range) | Not reached (1+–40+ months) | 40 months (1–33+) | Not reached (1–40+ months) |
| Relapses (duration of CR) | 3/14 (2,2,14 months) | 6/13 (1,1,3,5,6,11 months) | 9/27 (33%) |
| Median overall survival† (range) | Not reached (2–44+ months) | 41+ months (6–37+ months) | 22+ months (2–44+ months) |

*Placebo in cycles one and two, rhGM-CSF in cycles three to five (six). †Probability of DFS and overall survival. CR, complete remission; PR, partial remission; NR, no response; DFS, disease-free survival.

difference between the placebo and rhGM-CSF group with respect to the leucocyte nadir, but the difference in granulocyte nadir (0.39 versus 0.27/nl; $P < 0.05$) was significant. In group B, the leucocyte and granulocyte nadirs were significantly lower after cycles one and two (placebo) compared with cycles three to five (6) with rhGM-CSF (Table 3). In this group, the support by rhGM-CSF reduced the number of cycles with a granulocyte nadir <0.500/nl from 28/30 cycles (93%) to 20/37 cycles (54%) ($P < 0.0005$). The median duration of granulocytopenia <0.5/nl was significantly reduced from 4.5 days to 2 days by rhGM-CSF ($P < 0.01$) (Figure 1). In the rhGM-CSF-treated patients, the granulocytes showed a rapid increase 1 day after initiating rhGM-CSF administration and decreased to values similar to those in the placebo group on days 8–9 (Figure 1). There was no effect of rhGM-CSF on thrombocyte nadir or on duration of thrombocytopenia (Table 3). Comparing the first two chemotherapy cycles of both arms, there was no significant difference between the rhGM-CSF and the placebo group concerning the number of febrile neutropenic episodes or days >38°C and the days requiring systemic antibiotic therapy.

*Table 3. Peripheral blood counts (median, range) in patients treated with or without GM-CSF after chemotherapy with VACPE. The patients received rhGM-CSF (group A) or placebo (group B) during the first two cycles of chemotherapy. Afterwards, rhGM-CSF was administered to all patients*

| | Group A† (GM-CSF) | Group B‡ (placebo*) | |
|---|---|---|---|
| Leucocyte nadir (cells/nl) | | | |
| Cycles one and two (random) | 1.0 (0.2–2.3) | 0.9 (0.2–2.9) | n.s. |
| Cycles three to five (6) (rhGM-CSF) | 0.95 (0.1–7.3) | 1.55 (0.5–5.5) | n.s. |
| | n.s. | $P < 0.01$ | |
| Granulocyte nadir (cells/nl) | | | |
| Cycles one and two (random) | 0.39 (0.1–1.4) | 0.27 (0.0–1.1) | $P < 0.05$ |
| Cycles three to five (6) (rhGM-CSF) | 0.43 (0.0–3.6) | 0.5 (0.0–2.2) | n.s. |
| | n.s. | $P < 0.03$ | |
| Duration of granulopenia (<0.5/nl) | | | |
| Cycles one and two (random) | 2 (0–12) | 4.5 (0–10) | $P < 0.01$ |
| Cycles three to five (6) (rhGM-CSF) | 3 (0–13) | 1 (0–11) | n.s. |
| | n.s. | $P = 0.01$ | |
| Thrombocyte nadir (cells/nl) | | | |
| Cycles one and two (random) | 93 (8–247) | 103 (7–298) | n.s. |
| Cycles three to five (6) (rhGM-CSF) | 56 (5–257) | 69 (4–176) | n.s. |
| | n.s. | n.s. | |
| Duration of thrombocytopenia (<100/nl) | | | |
| Cycles one and two (random) | 1 (0–45) | 0 (0–22) | n.s. |
| Cycles three to five (6) (rhGM-CSF) | 4 (0–21) | 1 (0–18) | n.s. |
| | n.s. | n.s. | |

*Placebo in cycles one and two rhGM-CSF in cycles three to five (six). †The data represent 27 cycles of VACPE in group A during the first two cycles and 34 cycles of VACPE during cycles three to five (six). ‡The data represent 30 cycles VACPE in group B during the first two cycles and 36 cycles VACPE during cycles three to five (six). n.s., non-significant.

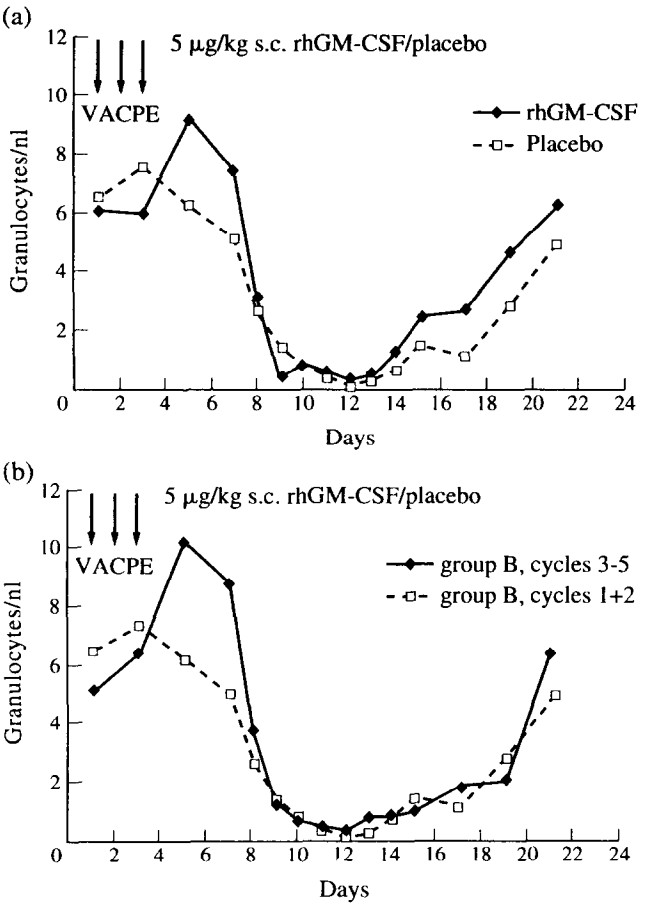


**Figure 1. Comparison of granulocytes during the first two cycles of VACPE (a) in the rhGM-CSF and placebo group after VACPE and comparison of granulocytes between the first two cycles placebo followed by rhGM-CSF in cycles three to five [6] (b). Prednisone was administered on days 1–7.**

The adverse events of rhGM-CSF were generally mild (Table 4). One patient, however, developed a severe anaphylactoid reaction immediately after rhGM-CSF injection requiring intervention by catecholamine therapy. The patient quickly recovered from this shock.

## DISCUSSION

In the chemotherapy of advanced or high-grade NHL, optimal regimens remain to be defined. It is still uncertain whether dose intensification including myeloablative therapy in combination with ABMT or PSCT may be associated with an impact on response rate or survival [1, 16, 17, 19, 35, 36]. On the other hand, there are some observations which imply that the prognosis may be related to dose intensity, at least in high-risk patients [36–40]. However, the major limiting toxicity of dose intensification is myelosuppression.

Haematopoetic growth factors allow the intensity of treatment to be increased or therapy-free intervals to be shortened [25, 27]. In this randomised pilot study, we investigated the effect of rhGM-CSF on the haematological toxicities following combined chemotherapy with VACPE in patients with high-grade NHLs [29, 41]. In a comparison of all initial parameters, no significant differences between treatment groups were observed, although the T-cell-derived lymphomas occurred predominantly in the placebo group. The leucocyte nadir did not differ between rhGM-CSF and placebo groups during the first two cycles, but the granulocyte nadir was significantly lower in the placebo group. The data suggest a possible slight benefit of rhGM-CSF for neutropenia in those who received rhGM-CSF only in cycles three to five (6). Despite known stimulatory effects of rhGM-CSF on megakaryotpoesis *in vitro* [22], *in vivo* there was no effect on thrombocyte nadir or duration of thrombocytopenia according to other reports using a similar dose schedule [23, 24, 27, 28]. Using higher doses, a potential dose-dependent effect on chemotherapy-induced thrombocytopenia is suggested by some data [28]. No effect of rhGM-CSF was observed on the incidence of neutropenia-related infectious complications. This may be due to the small number of patients within the two groups. Gerhartz and associates [27] reported a significant beneficial effect of rhGM-CSF regarding the frequency of infections in a phase III trial. Similar results were demonstrated for rhG-CSF in patients with solid tumours or leukaemias by administration of growth factors after chemotherapy [26, 40, 41].

No effect of rhGM-CSF was noted on response rate or survival, which may be due to the low number of patients and to the fact that all patients received rhGM-CSF after the second cycle of VACPE. Gerhartz and associates [27] reported an improved response in high-risk patients with NHLs using rhGM-CSF as supportive therapy. These results, however, did not translate into an improved overall survival rate.

The dose of 5 μg/kg body weight is within the range determined to be well tolerated and effective in phase I/II trials [44]. Indeed, adverse effects were rare and mild local skin reactions occurred during less than 5% of the administered cycles. The only severe adverse effect was an anaphylactoid-type reaction after rhGM-CSF, a known potential toxicity of rhGM-CSF and also described as a so-called first dose effect [45].

In conclusion, rhGM-CSF administered at a dosage of 5 μg/kg for 10 days after finishing chemotherapy reduced significantly the neutropenia and duration of neutropenia after VACPE. Its benefit for response induction and survival via rhGM-CSF-supported dose intensification remains to be determined.

*Table 4. Side-effects of rhGM-CSF in 177 cycles with rhGM-CSF*

| | WHO grade (%) | | |
|---|---|---|---|
| | 1 | 2 | 3/4 |
| Drug fever | 0.6 | 0.0 | 0.0 |
| Exanthema | 4.5 | 0.0 | 0.0 |
| Allergic reaction | 0.0 | 0.0 | 0.6 |
| Cardiac | 1.1 | 0.6 | 0.0 |
| Nausea | 0.6 | 0.6 | 0.0 |
| Pain of joints | 2.3 | 0.0 | 0.0 |

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