High dose treatment for haematologic malignancies: from rituals to evidence based practice
Mank, A.P.M.

Citation for published version (APA):
Mank, A. P. M. (2013). High dose treatment for haematologic malignancies: from rituals to evidence based practice

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 10

Ambulatory treatment after high dose chemotherapy with or without autologous stem cell transplantation is safe and feasible: a prospective evaluation of 6 years of home care

Arno Mank, Charlot Schoonenberg, Kim Bleeker, Susanne Heijmenberg, Koen de Heer, Rien van Oers and Marie José Kersten

Submitted
Abstract

Background: A prospective, non randomized clinical study was undertaken to examine the safety and feasibility of ambulatory care in patients undergoing consolidation chemotherapy for acute leukemia, or autologous stem cell transplantation for lymphoma or myeloma.

Design and Methods: Patients fulfilling the eligibility criteria were discharged into ambulatory care the day after the last chemotherapy administration, or the day after reinfusion of the stem cells. Patients were seen at the ambulatory care unit 3 times a week.

Results: During the study period, 224 patients were admitted for 283 chemotherapy cycles. 101 patients (116 cycles) were considered not to be eligible for the ambulatory care program, mostly because of their medical situation, the lack of a caregiver, or the travel time to the hospital. The 123 patients in the ambulatory care group, who underwent 167 cycles of high dose chemotherapy, were able to spend more than 70% of the neutropenic phase at home. In 44% of the cycles, patients were never readmitted to the hospital. There was no treatment related mortality during the ambulatory care period. The median costs per day for the ambulatory care group were less than 50% of the costs for the hospital group.

Conclusions: This study demonstrates the safety, feasibility and economic benefit of managing carefully selected patients in an ambulatory care setting after high dose chemotherapy with or without autologous SCT for several diagnoses. Patients and their caregivers felt safe and comfortable at home, and the vast majority preferred home care to in-hospital treatment.
Introduction

High dose chemotherapy with or without autologous stem cell transplantation (SCT) is standard practice for many hematologic malignancies. The main risks of intensive chemotherapy, with its subsequent prolonged pancytopenia, are infectious complications and bleeding.\(^1\) The toxicity and mortality associated with high dose chemotherapy have been reduced by several factors, such as the use of mobilized peripheral blood stem cells instead of bone marrow, the administration of granulocyte colony-stimulating factor, improved prophylactic and empiric antibiotic regimens, and a more proactive management in preventing opportunistic infections.\(^2\) Although protective isolation to prevent infections has long been the accepted standard of care for these patients, the necessity of keeping patients in hospital after myelosuppressive chemotherapy or SCT until full neutrophil recovery is under discussion.\(^3\)\(^-\)\(^4\).

Health care issues, quality of life and more efficient use of hospital resources have led to several projects implementing outpatient or home care even during high-risk phases of treatment. Ambulatory treatment has the potential to decrease patient exposure to multidrug-resistant organisms in the hospital and to provide a more comfortable environment for patients and their family.\(^5\) Ambulatory treatment should obviously first of all be safe regarding the risk of infection and it should not negatively affect overall survival.\(^6\) High dose chemotherapy with or without SCT is an expensive medical procedure.\(^7\) According to several studies hospital admission costs account for 58 to 78% of the total costs of high dose chemotherapy. Therefore, a shift from inpatient to outpatient treatment could lead to a substantial decrease in costs.\(^8\)-\(^10\)

Over the last 20 years different models for outpatient treatment have been developed for selected patients groups, e.g. following SCT. Patients were visited, and if necessary, treated at home or patients were seen in an ambulatory care setting in the hospital, in a separate unit or a hotel accommodation connected to the hospital. Some studies employing home-based\(^11\)-\(^16\) or ambulatory treatment\(^17\)-\(^21\) have shown ambulatory care to be safe. However, most of these studies were performed in a single hematologic malignancy with a limited amount of patients. Support, education, perception, expectations and feeling safe at home instead of being hospitalized are important topics in the development of an ambulatory care program.\(^22\) The psychosocial impact of at-home versus in-hospital treatment in SCT showed significantly higher scores for emotional wellbeing and global quality of life in the ambulatory care group.\(^23\)
In a previous study we have defined requirements for eligibility for ambulatory care after high dose chemotherapy. We found that, compared to induction treatment for AML, high risk myelodysplastic syndrome (HD-MDS) and myeloablative allogeneic SCT, relatively few complications were seen after consolidation chemotherapy for AML, HD-MDS and after autologous SCT in patients with relapsed lymphoma and MM. We therefore considered these patients to be the most suitable candidates for ambulatory care. In the present study we prospectively examined the safety in patients receiving high dose chemotherapy with or without autologous SCT support for consolidation in AML, Acute lymphoblastic leukemia (ALL), relapsed lymphoma and Multiple Myeloma.

Design and Methods

Study design
A prospective nonrandomized clinical study, with a study group (ambulatory care) and a control group (patients not eligible for ambulatory care, treated in the hospital).

Patients and Requirements for ambulatory care
All consecutive patients admitted to the Hematology Department of the Academic Medical Centre in Amsterdam (Netherlands) between September 2005 and September 2011 with a hematologic malignancy (AML, MDS, ALL, NHL, and MM) undergoing treatment with high dose chemotherapy were considered for participation in the ambulatory care project. Patients with acute leukemia were not eligible during the first induction cycle. Eligibility criteria for ambulatory care included: WHO PS ≤ 2, travel time from home to the hospital less than 60 minutes, availability of an educated caregiver for 24 hours a day, and patient understanding and acceptance of the procedures. At the time of actual discharge into ambulatory care, the following additional eligibility criteria were checked: patients should have no fever nor uncontrolled symptoms, adequate oral intake, no mucositis ≥ CTC grade 2, no uncontrolled diarrhea and/or vomiting, and no cardiac or respiratory distress. In addition, patients had to feel safe to leave the hospital. If ambulatory care was not possible patients were included in the control group.
Ambulatory care

Before starting this project an ambulatory unit was organized to provide assistance to up to four patients simultaneously. Specialized nurses (C.S and K.B.) were trained to educate the patients and caregivers, to check fulfillment of the requirements for ambulatory care and to perform the check-ups at the ambulatory care unit. Subsequently more nurses were educated by training-on-the job. All patients and their caregivers were informed about the procedures before making the choice between ambulatory care and hospital care. At home patients were instructed to check their own vital parameters including temperature, oral intake and body weight daily, and to return to the hospital immediately in case of fever and/or other signs of infection, bleeding or any other complication. If necessary, patients could consult the hematology nursing staff 24 hours per day. Patients were discharged into ambulatory care on the day following the last administration of chemotherapy or, in the case of ASCT, on the day after reinfusion of the stem cells. Patients visited the ambulatory care unit 3 times a week for monitoring of vital signs such as weight, temperature, pulse and blood pressure. In addition, oral intake was discussed with the patients, the mouth was inspected for signs of mucositis, the central venous catheter (CVC) was checked and, if necessary, cultures of the central venous line were taken. Surveillance cultures (peri-anal and nasopharyngeal swabs) were taken once a week, and on indication other cultures were performed (such as stool cultures). The complete blood count was checked and platelet and red blood cell transfusions were given when required. Patients were seen by a physician at least weekly and more often if necessary. Visits generally took 1-2 hours if no red blood cell or platelet transfusions needed to be given. During the period of neutropenia in hospital, patients were nursed preferably in a single room. Strict hygiene procedures including hand washing and the use of hand alcohol were followed by all personnel. Patients were discharged from ambulatory care or from the hospital to the outpatient department as soon as neutrophils had recovered to > 0.5 * 10^9/l and their clinical condition was considered to be satisfactory.

Infection prophylaxis and supportive care

All patients were given the same infection prophylaxis, which was started on the first day of high dose chemotherapy, and continued until neutrophil recovery. Gram negative prophylaxis consisted of ciprofloxacin 500 mg orally or 400 mg intravenously (i.v.) b.i.d. or, if ciprofloxacin-resistant gram negative
bacteria were present in the surveillance cultures, colistin orally 200 mg q.i.d. and cotrimoxazole 960 mg b.i.d. *Gram positive prophylaxis* consisted of oral feneticilline 250 mg q.i.d or penicillin 1 million units i.v. q.i.d. from day 7 after start of the chemotherapy or day 1 after ASCT. In case of penicillin allergy, clarithromycine 500 mg b.i.d. was prescribed. *Antifungal prophylaxis* consisted of amphotericin B oral suspension 500 mg q.i.d.. The efficacy of the prophylaxis was checked by weekly surveillance cultures of the perineum and throat.

**Indications for readmission**

Patients were readmitted in case of temperature ≥ 38.5 C, uncontrolled nausea, vomiting or diarrhea, mucositis grade ≥ 2, requirement of total parenteral nutrition (TPN), hemodynamic instability, pneumonia, cardiac and/or respiratory distress or any other situation which could not be handled at home. If necessary, a hospital bed was always available. In the event of fever, patients were fully evaluated by a physician. Blood cultures were taken both from a peripheral vein and from the CVC. Other appropriate cultures were taken on indication, and a chest X-ray was performed. As soon as the situation had stabilized and the patient no longer required intravenous antibiotics, he or she could be discharged into ambulatory care again.

**Empiric antibiotic regimen**

In case of fever, patients were treated empirically with vancomycine 1000 mg i.v. b.i.d and ceftazidime 1000 mg i.v. t.i.d, or with other antibiotics based on results of the surveillance cultures (e.g. gentamycin or meropenem). Patients with persistent fever despite i.v. antibiotic therapy after 72 hours underwent evaluation for invasive aspergillosis by high resolution CT scan and galactomannan antigen testing in serum. If abnormalities were found, a bronco-alveolar lavage was performed for galactomannan antigen testing and culture of the broncho-alveolar fluid.

**Definitions and diagnostic criteria**

*Neutropenia*: absolute neutrophil count (ANC) < 0.5 x 10^9 /L.

*Fever*: a single oral temperature of ≥ 38.5°C not related to transfusion or drug administration.

*Infection*: Episodes of neutropenic fever (NF) were classified into four groups: 1. fever of unknown origin (FUO): fever without signs and symptoms
of inflammation at anatomic sites and no identification or recovery of pathogens, 2. clinically suspected infection (e.g. pneumonia) without documentation of a pathogenic microorganism (CDI), 3. microbiologically documented infection (MDI) with or without bacteraemia. This group included infections with coagulase-negative Staphylococcus (CNS), in which case at least two positive blood cultures were required, 4. invasive pulmonary aspergillosis (IPA), further classified according to the revised European organization for research and treatment of cancer and infectious diseases mycoses study group (EORTC/MSG) criteria which revised the definition of proven, probable or possible. 28

**Performance status:** the performance status (PS) was scored according to the WHO score (from 0, normal activity without restrictions, to 4, completely disabled and/or fully dependent in activities of daily living (ADL). 29

**Mucositis:** The severity of oral mucositis was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3.0, grading from 0 (no symptoms) to 4 (necrosis and/or alimentation not possible). 30 A score of 2 or more was considered to be a reason not to discharge patients because of the associated treatment and pain management.

**Calculation of costs**

For the purpose of the study, we looked at costs of admission versus costs of ambulatory visits. The costs were calculated from the day of the start of the (possible) ambulatory care until the day of discharge to the outpatient department. In-hospital hematological admission in our hospital is charged at € 491, - per day. A visit to the ambulatory care unit for a regular check-up was calculated at € 65, -. In case of blood transfusions, visits lasting more than 2 hours were considered to be day care and were charged at € 423, - per visit. This calculation does not include the costs of diagnostic procedures, laboratory services, medication, blood products and overhead costs, since they were expected to be similar for both groups. Also, loss of income to patients and caregivers and costs of daily living at home were not included in the analysis.

**Patient satisfaction**

The first 64 patients who participated in the ambulatory care group were invited to complete an anonymous questionnaire after completion of the whole procedure. On a psychometric 5-point symmetric Likert scale, patients specified their level of agreement or disagreement for a series of
21 statements. This questionnaire covered the following topics: logistics, information, communication and patient perception.

**Statistical methods**

The incidence and types of complications requiring readmission to hospital, and the number of hospital days saved by this policy have been prospectively evaluated.

Results were compared with those observed in the control group of patients who were treated in the hospital.

The following factors were descriptively analyzed for home care versus hospital care: number of days until neutrophil recovery, (re-)admission, fever and infection, performance status, mucositis, nutrition, weight difference between start and end of the treatment, platelet and erythrocyte transfusions and patient satisfaction. All analyses were carried out using SPSS version 18 statistical software (SPSS Inc, Chicago, IL).

**Results**

**Reasons for inclusion in the ambulatory care or hospital group**

Two hundred and twenty four patients undergoing two hundred and eighty three cycles of high dose chemotherapy (with or without ASCT) were included in the study. 123 patients (167 cycles) were included in the ambulatory care group and 101 patients (116 cycles) were included in the hospital group.

The most common reason for a patient during a particular cycle not to be included in the ambulatory care program was that he or she was considered to be medically unfit (63 cycles), most frequently because of fever. Logistic reasons (lack of a caregiver, travel time to the hospital) and patient preferences (53 cycles) were the other most prevalent reasons for not including patients in the ambulatory care program (figure 1).

**Baseline characteristics**

The patient characteristics including diagnosis and treatment are described in table 1, with AML/ high risk MDS being the most frequent diagnosis. There was no difference in the male to female ratio between both groups but there was a difference in age, with a higher median age in the hospital group of 57 years (range 19-72) versus 49 years (range 18-68) in the ambulatory care group. The included treatment modalities also show several
striking differences. In both groups, the most commonly included treatment was consolidation chemotherapy for AML (34% of all cycles included in the ambulatory care group and 46% in the hospital group). However 75% of all 36 BEAM cycles and 93% of all 44 patients treated with high dose chemotherapy for NHL were treated in the ambulatory care group, whereas
68% of 71 patients were treated with high dose melphalan for MM were treated in the hospital group (table 1).

Readmissions in the ambulatory care group

In 73 cycles (44% of all cycles), patients treated in the ambulatory care group were never readmitted. Of the 108 readmissions, 82 were single readmissions; in 10 cycles patients were readmitted twice and two patients had to be re-admitted three times. Fever was the most frequent reason for readmission (58%), followed by mucositis (14%), diarrhoea (7%) and respiratory distress (6%). In 17% of the readmissions, there were multiple reasons for readmission.

In the ambulatory care group 71% of the 2812 days which would otherwise have been spent in the hospital could be spent at home. If readmission was necessary, the median day of readmission was day 8 (range 2-27) while the median duration of readmission was 6 days (range 1-22). The highest risk of readmission was observed following consolidation treatment for AML (72%) and following BEAM/autologous SCT (70%). The risk of readmission for patients treated with high dose chemotherapy for ALL, NHL, and MM was 37%, 44% and 39%, respectively.

Outcome variables (mucositis, weight loss, fever and infections)

In table 2 the outcome variables, including fever and infection are summarized. The total number of patient days in the ambulatory care group was 2812 days, with a median of 14 days per cycle (range 6-40). Many of the patients needed platelet transfusions (84%) and red blood cell transfusions (79%).

In 62% of the cycles one or more febrile episodes occurred. In approximate two-third of the febrile episodes, the febrile episode was classified as FUO (fever of unknown origin). An overview of the different micro-organisms which were identified is shown in table 2. From the 27 gram-positive isolates, 70% (19) coagulase negative staphylococci were isolated, and 2 Streptococcus Mitis. From the Gram-negative isolates Escheria coli (4) and Pantoea spec. (1) found. In seven cases possible IPA was determined, in one case probable. The median number of days using IV antibiotics was 3 days with a range of 0-32 days.

Two patients from the ambulatory care group had to be admitted temporarily to the ICU and both recovered fully. One patient was admitted for 48 hours because of hemodynamic instability following a CNS bacteremia, and the second patient for 24 hours because of a severe
an anaphylactic reaction to a platelet transfusion. No deaths occurred in the ambulatory care group, whereas 3 patients died of treatment-related complications in the hospital group.

**Calculation of costs and use of hospital beds**

In the hospital group, the total costs were calculated at €991.820,- (2020 days of admission at €491,- per day. The cumulative costs for the 2812 patient days in the ambulatory care group were considerably lower at
€ 505.184,- (783 days of admission at € 491.- per day; 182 days of day care at € 423.- per day and 673 regular visits to the ambulatory care unit at € 65.- per visit. The median costs per day were also lower for the ambulatory care group: € 180.- per day versus € 490.- in the hospital group. When comparing costs for relatively homogeneous group of AML/MDS patients undergoing consolidation chemotherapy, the median costs for the 1278 patients days in the ambulatory care group were € 209.- per day, versus € 491.- per day for the 1160 admission days for the hospital group. Apart from these direct cost savings shifting to ambulatory care treatment also meant more patients could be treated at our department: patients who otherwise would have been hospitalized were actually at home for 2029 days, implying that at a median duration of admission including chemotherapy and neutropenic phase of 22 days, 92 more patients could be admitted for high dose chemotherapy in this time period.

Patient satisfaction

Sixty four patients out of the first 89 patients in the study (72%) sent back the questionnaire. Four of the answers reflecting the topics logistics, information, communication and patient perception are shown in figure 2. All patients felt safe at home regarding the risk for infections and did not regret the decision to be treated at home. All patients, except for one, were positive about the logistics of ambulatory care. However, 15% of the
patients and their caregivers felt it to be somewhat burdensome to come
to the hospital for a check-up 3 times a week. Except for one patient all
patients would choose again for ambulatory care if necessary, and would
advise it also to fellow patients.

Discussion

In this prospective study of patients with AML, ALL, NHL and MM receiving
high dose chemotherapy with or without autologous stem cell support,
we examined whether ambulatory care could be a safe and more patient-
friendly alternative for hospital care.

All patients who were potentially eligible were carefully evaluated for
ambulatory care using a series of both medical and psychosocial criteria, and
an analysis of the situation at home.

Ultimately, in approximately 70% of the eligible cycles patients could be
treated at home, and they were able to spend more than 70% of the days
which normally would have been spent as an in-patient in their home
environment. Although readmission was necessary in 56% of the cycles,
which is comparable with other studies\textsuperscript{11, 14, 16, 19}, none of the patients had
life threatening complications and there was no treatment-related mortality.
Several outcome variables, such as number of days with fever, mucositis,
weight loss and use of TPN appeared to be more favorable in the patients
treated at home versus the patients who stayed in hospital, we were
reluctant to perform a formal comparison. The main reason for this caution
is the fact that since this was not a randomized trial, and patients were
selected on the basis of medical and logistic criteria, there were some
striking differences in the patient categories between the groups. Patients
who ended up in the ambulatory care group were younger and more often
had NHL or ALL, whereas in the hospital group patients were older and
more often had myeloma. This meant that also the treatment (e.g. BEAM
versus HDM) was different, and that it was thus impossible to have paired
groups for analysis. Secondly, the strict and cautious selection of the patients
which we applied might have provided bias in this study, because patients
in better medical condition were more likely to be treated in the ambulatory
care project.

Nonetheless, it is clear that ambulatory care is cost saving, and, importantly,
that better use can be made of hospital resources, because more patients
requiring intensive hematologic care could be treated at our hematology
department.
Results of the patient survey showed that patients feel safe, confident and comfortable at home and that the vast majority would again choose for ambulatory care if necessary, or would recommend it to other patients. It was however considered to be somewhat burdensome to come to the hospital 3 times per week. Also, we found it to be important to give intensive support also to the caregivers, who felt it to be a great responsibility to care for their spouses/family members. We found it to be extremely important that the team of physicians and nurses is well trained and experienced, and that a lot of time and effort is spent to educate the patients and their caregivers, both before and during the ambulatory treatment.

In conclusion, this study demonstrates the safety and feasibility of managing carefully selected patients in their home environment following high dose chemotherapy with or without autologous stem cell support. Ambulatory care is a cost saving and excellent alternative for hospital care, which, importantly, is also greatly appreciated by patients.

Acknowledgements
The authors would like to thank the patients and caregivers who participated in this study. Caroline Visser, micromiologist and Bart Biemond, hematologist for their contribution to the manuscript. We also thank all the nurses (especially Aline Coenraadts, former head nurse), physicians and other staff who treated patients in this study. Hans van der Lelie, former staff member of the Department of Hematology at the Academic Medical Centre, is acknowledged for his strong belief in this project and for providing the basis for ambulatory care at our hospital.
References


