Transfusion-associated iron overload as a predictive factor for poor hematopoietic stem cell mobilization in patients with hematologic malignancies

Park In Hae

Department of Medicine

The Graduate School, Yonsei University

Transfusion - associated iron overload as a predictive factor for poor stem cell mobilization in patients with hematologic malignancies

Directed by Professor Min, Yoo Hong

The Master's Thesis
submitted to the Department of Medicine
the Graduated School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Park In Hae

June 2007

This certifies that the Master's Thesis of
Park In Hae is approved.

Thesis Supervisor : Min Yoo Hong

Thesis Committee Member : Yang Woo Ick

Thesis Committee Member : Lyu Chuhl Joo

The Graduate School
Yonsei University

June 2007

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who gave me the possibility to complete this thesis. Especially, I would like to give my special thanks to my family whose love enabled me to complete this work. I am deeply indebted to my supervisor Prof. Min whose stimulating suggestions and supervision helped me in all the time of research for and writing of this thesis.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

Abstract

Transfusion-associated iron overload as a predictive factor for poor stem cell mobilization in patients with hematologic malignancies

Park, In Hae

Department of Medical Science
The Graduate School, Yonsei University

(Directed by Professor Min, Yoo Hong)

Background and Objective

Transfusion-associated iron overload is often observed in patients with hematologic malignancies. I analyzed the effect of iron overload, indicated by high serum ferritin level, on the mobilization of CD34+ peripheral blood stem cells (PBSC).

Patients and Methods

I evaluated the association between the serum ferritin level prior to PBSC collection and the number of $CD34^+$ cells collected through leukaphereses in fifty-one patients with various hematologic malignancies. Patients with serum ferritin level over 1,000ng/mL were defined as high ferritin group.

Results

Comparing the good ($\geq 1\times10^6$/kg CD34+ cells) and poor ($< 1\times10^6$/kg CD34+ cells) mobilizing groups, there was no difference in age, disease status, marrow involvement, number of previous chemotherapies, and white blood cell count at the first day of apheresis. However, there was a significant difference in the median units of transfused red blood cells between the good and poor mobilizer (2 vs. 8 units; p=0.012). Serum ferritin level was notably higher in the poor mobilizer (1,670 ± 1,320 ng/mL) compared with the good mobilizer (965 ± 705 ng/mL; p=0.035). Mean number of $CD34^+$ cells/kg collected per apheresis procedure was significantly lower in the high ferritin group compared to the low ferritin group (2.0 ± 1.4 *vs.* 7.4 ± 5.8, p=0.001). The cumulative number of

$CD34^+$ cells/kg collected during the whole procedure was also significantly lower in the high ferritin group (5.5 ± 4.7 *vs.* 13.1 ± 9.1, p=0.01). Multivariate analysis revealed that serum ferritin level remained as an independent predictive factor for poor PBSC mobilization.

Conclusions

The study indicated that transfusion-associated iron overload is a predictive factor for poor PBSC mobilization. Iron chelation therapy prior to apheresis may be required to collect sufficient numbers of PBSCs in the iron-overload patients.

Key Words : transfusion, iron overload, stem cell mobilization

Transfusion-associated iron overload as a predictive factor for poor stem cell mobilization in patients with hematologic malignancies

Park In Hae

Department of Medical Science
The Graduate School, Yonsei University

(Directed by Professor Min Yoo Hong)

Introduction

Mobilized peripheral blood stem cells (PBSC) are usually used for autologous hematopoietic stem cell transplantation (ASCT) in hematologic malignancies including malignant lymphoma, multiple myeloma as well as acute leukemia.[1,2] Since the infused stem cell dose is one of the important variables affecting successful hematologic recovery,[3,4] the ability to collect adequate numbers of PBSC is of critical importance for ASCT. It has been suggested that infusion of more than 2.0 - 2.5 x 10^6 CD34-positive (CD34+) cells/kg is sufficient for successful engraftment after myeloablative therapy.[5,6] In contrast, poor mobilization of PBSC is associated with poor transplantation outcomes after ASCT for a variety of hematologic malignancies.[6-8]

Several studies have shown that about 15-40% of patients have failed to mobilize a sufficient number of autologous PBSC for collection.[9,10] It has been demonstrated that the variables predicting poor stem cell mobilization include advanced age, disease entities, extensive prior cytotoxic therapies, secondary myelodysplastic change, disease invasion of the bone marrow, and mobilizing strategies used for PBSC collection.[9,11,12] However, several other studies have failed to demonstrate an association of these factors with poor PBSC mobilization.[7,9] PBSC mobilization is not successful even in a subset of healthy donors given recombinant human granulocyte colony-stimulating factor (G-CSF) as the mobilization stimulus.[13,14] These findings strongly suggest that factors other than malignancy and prior therapies may affect mobilization.

Chronic red blood cell transfusion in patients with hematologic malignancies is often necessary. However, it may cause iron overload and its complications.[15] Excessive iron can cause serious cellular and tissue damages through formation of highly reactive hydroxyl radicals.[16] Such free radicals can damage proteins, lipids and DNA, leading to destruction of organelles, cell death, and tissue fibrosis. The clinical effects of excessive tissue iron include heart disease, hepatic dysfunction, and derangement of endocrine system.[17]

The influences of iron overload on the regulation of hematopoiesis and immunity have not yet been fully elucidated. An *in vitro* study suggested that ferritin had an inhibitory effect on the proliferation of human hematopoietic progenitor cells and T lymphocytes and differentiation of human B lymphocytes into antibody-producing cells.[18] Negative effects of transfusional iron overload on immune system, causing susceptibility to infections, were also been recently demonstrated.[18] Especially for patients with hematologic malignancies undergoing hematopoietic stem cell transplantation, iron overload could be a significant contributor to treatment-related mortality.[19,20] In this study, I evaluated the effect of transfusion-associated iron overload on the PBSC collection in patients with hematologic malignancies.

Patients and Methods

Study population

I retrospectively analyzed a total of 51 patients undergoing PBSCs collection between January 2000 and December 2006. The underlying diseases were multiple myeloma (n=18), malignant lymphoma (n=25), and acute myeloid leukemia (n=8). To exclude the hyperferritinemia due to other causes, such as infection, connective tissue disease and liver disease, patients with active infection or liver disease were excluded from the study. All patients signed written informed consent and were treated at the Yonsei University Health System. In all patients, serum levels of ferritin, transferrin iron binding capacity (TIBC), iron and C-reactive protein (CRP) were examined on the first day of leukapheresis. Finally, patients with serum CRP level more than 6mg/dL were excluded from the analysis due to the possibilities of undetectable infection or inflammation. Patients with serum ferritin levels over 1,000 ng/mL, and with a history of red blood cell transfusions prior to stem cell collection were defined as a group having transfusion-associated iron overload. This retrospective study was approved by the Severance Hospital Institutional Review Board.

Mobilization regimens

Fifty patients received mobilizing chemotherapy plus recombinant human G-CSF (Neutrogen; Choongwae Pharmaceutical., Seoul, Korea) to mobilize and collect PBSC. One patient received G-CSF alone for mobilizing purpose. The chemotherapy regimens were heterogeneous and categorized as etoposide-based (n=22), high dose cyclophosphamide (n=6), etoposide plus cyclophosphamide based (n=14) and other drug combinations (n=9). For all patients, subcutaneous administrations of G-CSF (300 μg/day) were commenced from the first day of neutropenia (neutrophils count < 0.5 x 10^9/L) until the completion of the PBSC harvest.

PBSC collections

Apheresis was started immediately when the white blood cell count exceeded 3.0 x 10^9/L after mobilization chemotherapy. Collection of PBSC was performed using a large-volume leukapheresis (LVL) procedure (4 blood volumes processed) with a blood cell separator (COBE Spectra 7.0, COBE BCT Inc., Lakewood, CO, USA) as previously described.[21] Autologous PBSCs were cryopreserved until reinfusion for ASCT.

Flow cytometry assay for $CD34^+$ cells enumeration

The $CD34^+$ cell counting was carried out using the ProCOUNT Progenitor Cell Enumeration from Becton Dickinson (BD Biosciences, San Jose, CA, USA). Briefly, 50 μL of leukapheresis product was incubated with control antibodies and anti-CD34 antibody from the ProCOUNT™ kit from Becton Dickinson. The acquisition and analysis of the data were performed using a flow cytometer (FACSCalibur; Becton Dickinson).

Statistical analysis

Patients with transfusion-associated iron overload (serum ferritin level over 1,000 ng/mL) were defined as the high ferritin group; remaining patients were defined as the low ferritin group. Poor mobilizers were defined as patients for whom the required number of $CD34^+$ cells/kg per LVL (1 x 10^6/kg) was not collected. Successful mobilization was defined as cases where the total number of $CD34^+$ cells obtained with whole procedures was over 2.5 x 10^6/kg. All statistical analyses were done using SPSS ver.12 (SPSS, Chicago, IL, USA). Two-tailed compared *t*-tests were used for continuous variables, *chi-square* tests for categorical variables and multiple logistic regression tests for multivariate analysis. Statistical significance was defined as $p<0.05$.

Results

Patients' characteristics according to mobilization extent

Comparison of the good and poor mobilizing groups revealed no difference in sex, age, disease entities, disease status at harvest, bone marrow involvement, number of previous chemotherapies, and platelet counts at the first day of leukapheresis (Table 1). White blood cell counts at the first day of apheresis were not different between the good mobilizer group (10.2 ± 7.5 x 10^9/L) and the poor mobilizer group (16.4 ± 15.6 x 10^9/L). Additionally, no difference was observed in the number of $CD34^+$ cells harvested among the different mobilizing regimens utilized, which mainly consisted of etoposide- and cyclophosphamide-based protocols. However, the number of $CD34^+$ cells/μL in the peripheral blood at the first day of harvest was significantly lower (7 ± 5 /μL) in the high ferritin group compared with that (73 ± 54 /μL) of the low ferritin group (Table 1). In line with these findings, there was a significant difference in the number of $CD34^+$ cells per the first round of apheresis (0.6 ± 0.4 × 10^6/kg for poor mobilizer vs. 8.2 ± 5.2 × 10^6/kg for good mobilizer; $p<0.001$) and total number of $CD34^+$cells collected (2.7 ± 2.0 × 10^6/kg for poor mobilizer vs. 14.7 ± 9.1 × 10^6/kg for good mobilizer; $p<0.001$.

There was a remarkable difference in the amount of transfused red blood cell between the good and poor mobilizer (2 units vs. 8 units; $p=0.01$). In connection with these findings, serum ferritin levels were significantly higher in the poor mobilizer group (1,670 ± 1,320 ng/mL) compared with the good mobilizer group (965 ± 705 ng/mL; $p=0.03$) (Table 1).

Table 1. The characteristics of patients according to mobilization extent

Factors	Good mobilizer (N=34)	Poor mobilizer (N=17)	*P* value
Sex (M/F)	16/18	8/9	NS
Median age (yr, range)	47 (16-69)	43 (17-64)	NS
Disease entities (lymphoma/multiple myeloma/AML*)	16/15/3	9/3/5	NS
Status at harvest (complete remission/advanced)	19/15	11/6	NS
Bone marrow involvement at harvest	2	1	NS
Number of prior chemotherapy (median, range)	4 (1-8)	4 (2-9)	NS
Platelet count at harvest ($x10^9$/L, mean±SD)	90±56	88±58	NS
Amount of pRBC transfusion (median unit , range)	2 (0-20)	8 (1-20)	0.012
Serum ferritin (ng/mL, mean±SD)	965±705	1,670±1,320	0.035
Mobilizing regimens			
Etoposide-based	13	9	NS
High dose cyclophosphamide	4	2	NS
Combined†	12	2	NS
Others‡	5	4	NS
Number of apheresis cycles (median, range)	2 (1-4)	3 (2-11)	<0.001
WBC count at 1st harvest day ($x10^9$/L, mean±SD)	10.2±7.5	16.4±15.6	0.061
CD34+ cells in PB¶ at 1st harvest day (/uL, mean±SD)	73±54	7±5	<0.001
CD34+ cells/kg/apheresis ($x10^6$/kg, mean±SD)	8.2±5.2	0.6±0.4	<0.001
Total CD34+ cells collected ($x10^6$/kg, mean±SD)	14.7±9.1	2.7±2.0	<0.001

*, acute myeloid leukemia; †, DECP (dexamethasone / etoposide / cyclophosphamide / cisplatin) or D-PACE (dexamethasone / cisplatine / adriamycin / etoposide / cyclophosphamide); ‡, IVAM (vincristine / methotrexate / cytarabine / ifosphamide), VAD (vincristine / adriamycin / dexamethasone), DHAP (cisplatine / cytarabine / dexamethasone), or MICMA (mitoxantrone / carboplatine / cytarabine / prednisolone); ¶, peripheral blood.

Patients' characteristics according to serum ferritin level

Sixteen patients (31%) were categorized in the high ferritin group and 35 (69%) patients were categorized in the low ferritin group. The mean value of serum ferritin was 2,343 ng/mL in the high ferritin group, which was significantly higher than that (678 ng/mL) in the low ferritin group (p<0.001). The mean serum iron level was 123 ug/dL in the low ferritin group, which showed a statistical difference comparing with that (188 ug/dL) of the high ferritin group (p<0.001). Comparing the low and high ferritin groups, there was no difference in sex, age, disease status at harvest, bone marrow involvement, number of previous chemotherapy, or serum level of CRP (Table 2). No difference was observed in the types of mobilizing regimens according to serum ferritin levels. White blood cell counts at the first day of apheresis were not different between the low ferritin group ($14.6 \pm 14.4 \times 10^9$/L) and the high ferritin group ($11.2 \pm 9.4 \times 10^9$/L). In contrast, platelet counts at the first day of apheresis were significantly higher in the low ferritin group compared with those of the high ferritin group ($105 \pm 61 \times 10^9$/L vs. $57 \pm 23 \times 10^9$/L; p<0.001). I found that the median unit of transfused red blood cell was significantly higher in the high ferritin group (median, 12 units; range, 8-20 units) compared with that of the low ferritin group (median 1 unit; range, 0-7 units; p<0.001) and the serum ferritin level was observed a significant correlation with the amount of transfused red blood cells (r=0.692, p<0.001).

Table 2. The characteristics of patients according to serum ferritin level

Factors	Low ferritin group (N=35)	High ferritin group (N=16)	*P* value
Sex (M/F)	18/17	6/10	NS
Median age (yr, range)	47 (16-64)	42 (17-69)	NS
Disease entities (lymphoma/multiple myeloma/AML*)	18/17/0	7/1/8	NS
Status at harvest (complete remission/advanced)	19/16	11/5	NS
Bone marrow involvement at harvest	3	0	NS
Number of prior chemotherapy (median, range)	4 (2-9)	3 (1-9)	NS
Platelet count at harvest ($x10^9$/L, mean±SD)	105±61	57±23	0.004
Amount of pRBC transfusion (median unit, range)	1 (0-7)	12 (8-20)	<0.001
Serum ferritin (ng/mL, mean±SD)	678±467	2,343±1,323	<0.001
CRP** (mg/dL, mean±SD)	1.8±1.5	1.8±1.4	NS
Mobilizing regimens			
Etoposide-based	13	9	NS
High dose cyclophosphamide	4	2	NS
Combined†	13	1	NS
Others‡	5	4	NS
Number of apheresis cycles (median, range)	2 (1-11)	3 (2-7)	0.098
WBC count at 1st harvest day ($x10^9$/L, mean±SD)	11.2±9.4	14.6±14.4	NS
CD34+ cells in PB¶ at 1st harvest day (/uL, mean±SD)	67±54	16±14	0.001
CD34+ cells/kg/apheresis ($x10^6$/kg, mean±SD)	7.4±5.8	2.0±1.4	0.001
Total CD34+ cells collected ($x10^6$/kg, mean±SD)	13.1±9.1	5.5±4.7	0.010

*, acute myeloid leukemia; **, C-reactive protein; †, DECP (dexamethasone / etoposide / cyclophosphamide / cisplatin) or D-PACE (dexamethasone / cisplatine / adriamycin / etoposide / cyclophosphamide); ‡, IVAM (vincristine / methotrexate / cytarabine / ifosphamide), VAD (vincristine / adriamycin / dexamethasone), DHAP (cisplatine / cytarabine / dexamethasone), or MICMA (mitoxantrone / carboplatine / cytarabine / prednisolone); ¶, peripheral blood.

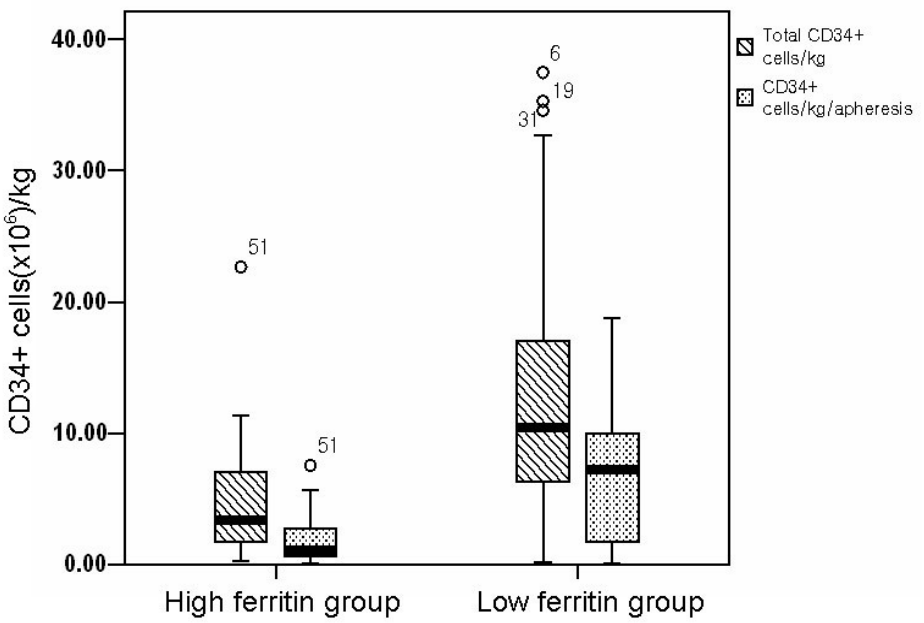

Figure 1. Comparison CD34+ cells harvested between high ferritin group and low ferritin group. Oblique lined bars represented total collected CD34+ cells (x 10^6/kg), which showed a statistical difference between two groups (p=0.010). Dotted bars represented CD34+ cells collected per one cycle of apheresis and it also had a significant difference according to ferritin level (p=0.001).

PBSCs mobilization in relation to serum ferritin levels

There was no difference in the median number of apheresis between the low and high ferritin groups. However, the number of $CD34^+$ cells/μL in peripheral blood at the first day of harvest was significantly lower (16 ± 14 /μL) in the high ferritin group compared with that of the low ferritin group (67 ± 54 /μL, p=0.001). Mean number of $CD34^+$ cells/kg collected per apheresis procedure was significantly decreased in the high ferritin group compared to that of the low ferritin group (2.0 ± 1.4 *vs.* 7.4 ± 5.8, p=0.001). The cumulative number of $CD34^+$ cells/kg collected during the whole procedure was also significantly low in the high ferritin group (5.5 ± 4.7 *vs.* 13.1 ± 9.1, p=0.01) (Figure 1). The rate of successful mobilization, as defined by collection of over 2.5×10^6/kg $CD34^+$ cells with the whole apheresis, was significantly low in the high ferritin group (66.7% vs. 91.4%; p=0.043). Multivariate analysis revealed that serum ferritin levels, together with low platelet count, remained as independent predictive factors for poor hematopoietic stem cell mobilization (Table 3).

Table 3. Multivariate analysis of predictive factors for successful stem cell mobilization

Factors	***P* value**	**Odds radio (CI 95%)**
Age	0.65	0.91 (0.91-1.01)
Disease entities	0.17	7.73 (0.43-142.12)
Disease status at harvest	0.72	0.74 (0.11-4.65)
Burden of previous chemotherapy	0.10	1.53 (0.90-2.34)
Platelet count	0.06	1.01 (1.00-1.29)
High serum ferritin level	0.05	7.81 (1.01-61.71)

Discussion

This study revealed that transfusion-associated iron overload is a predictive factor for poor hematopoietic stem cell mobilization in patients with hematologic malignancies. Substantial differences in the concentration of $CD34^+$ cells in the leukapheresis products among patients following a mobilization procedure have been reported.[9,11,12,13] The incidence of poor mobilizing population was variable to range from 15 to 40% in different subsets of patients.[9]

The dose of CD34+ cells has been reported to influence post-transplant morbidity and overall survival following ASCT.[3,7] In a study of 262 consecutive patients who underwent ASCT for Hodgkin's and non-Hodgkin's lymphomas, low numbers of infused $CD34^+$ cells were associated with both progression and death.[7] Identification of predictive factors for poor mobilizing patients is of value both for providing insight into the mechanism of mobilization and for selection of patients who may not benefit from a mobilization approach.

In this study, poor stem cell collections were documented in approximately twenty percent of cases undergoing leukapheresis. Comparing the good and poor mobilizing groups, there was no difference in sex, age, disease entities, disease status at harvest, bone marrow involvement, number of previous chemotherapies or platelet counts at the first day of leukapheresis. In addition, no difference was also observed in terms of $CD34^+$ cells harvested among the different mobilizing regimens utilized, which consisted primarily of etoposide- or cyclophosphamide-based protocols.

Surprisingly, there was a statistical difference in serum ferritin levels and in the number of red blood cell units transfused prior to leukapheresis between the poor and good mobilizing groups. The unit number of red blood cells transfused and the mean serum ferritin levels in the poor mobilizer group were significantly higher compared with the good mobilizer group.

With respect to iron overload, we could not find any differences in sex, age, disease status, and previous burden of chemotherapies or radiotherapy, marrow

involvement at the harvest, serum CRP titer, or mobilizing regimens between the low and high ferritin groups. As expected, the median value of red blood cell units transfused was significantly higher in the high ferritin group compared to the low ferritin group. To eliminate the possibilities of hyperferritinemia due to other causes, patients with infection, inflammation or higher serum CRP titer (≥ 6 mg/dL) were excluded from the study.

There was no difference in white blood cell counts at the first day of harvest or the number of apheresis between the low and high ferritin groups. However, the number of $CD34^+$ cells/μL in peripheral blood at the first day of harvest was significantly lower in the high ferritin group compared with that of the low ferritin group. Both the number of $CD34^+$ cells/kg per each apheresis and total number of $CD34^+$ cells/kg collected were significantly lower in the high ferritin group. Multivariate analysis indicated that serum ferritin level prior to the initiation of leukapheresis remained as an independent predictive factor for poor hematopoietic stem cell mobilization.

The mechanisms underlying the negative effects of iron overload on the mobilization of stem cells will require further investigation. One possibility is that the expression and functional status of adhesion molecules such as lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1(ICAM-1) may be altered on the hematopoietic stem cells by iron overload, since it has been demonstrated that the most significant difference between the good and the poor mobilizing groups was the percentage of cells expressing the ligand-receptor pair of LFA-1 and ICAM-1.[22,23] It is also possible that functional ligand-receptor interactions between the hematopoietic stem cells and bone marrow niche, including stromal cell derived factor-1 (SDF-1) and its receptor (CXCR4),[24] vascular cell adhesion molecule-1 (VCAM-1)/CD49A,[22] P-selectin glycoprotein ligand-1 (PSGL)/CD62L,[25] and Kit/c-kit ligand,[26] may be potentially affected by iron overload. In conclusions, my study reveals that transfusion-associated iron overload was significantly associated with poor PBSC

mobilization in patients with hematologic malignancies. Evaluation of iron overload status prior to ASCT may be very important for identifying patients at high risk of poor mobilization and who may not benefit from high-dose therapy and ASCT. In addition, effective iron chelation therapy may be an optimal strategy to allow for collection of sufficient numbers of PBSC for ASCT in patients with history of multiple transfusions.

Conclusion

In this study, I analyzed the effect of iron overload on the mobilization of CD34+ peripheral blood stem cells (PBSC). I evaluated the association between the serum ferritin level prior to PBSC collection and the number of $CD34^+$ cells collected in fifty-one patients with various hematologic malignancies. Mean number of $CD34^+$ cells/kg collected per apheresis procedure and the cumulative number of $CD34^+$ cells/kg collected during the whole procedure were significantly lower in the high ferritin group compared to those of the low ferritin group. Multivariate analysis revealed that serum ferritin level remained as an independent predictive factor for poor PBSC mobilization.

My study indicated that transfusion-associated iron overload is a predictive factor for poor PBSC mobilization. Iron chelation therapy prior to apheresis may be required to collect sufficient numbers of PBSCs in the iron-overload patients.

Reference

1. Strehl J, Mey.U, Glasmacher A, Djulbegovic B, Mayr C and Gorschluter M. *High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis.* Haematologica 2003;**88**:1304-15.
2. van Besien K, Loberiza Jr. FR, Bajorunaite R, Armitage JO, Bashey A, Burns LJ, et al. *Comparision of autologous and allogenic hematopoietic stem cell transplantation for follicular lymphoma.* Blood 2003;**102**:3501-29.
3. Perez-Simon JA, Martin A, Caballero D, Corral M, Nieto MJ, Gonzalez M, et al. *Clinical significance of CD34+ cell dose in long-term engraftment following autologous peripheral blood stem cell transplantation.* Bone Marrow Transplant 1999;**24**:1279-83.
4. Weaver CH, Hazelton B, Birch R, Palmer P, Allen C, Schwartzberg L, et al. *An analysis of engraftment kinetics as a function of the CD34 content of peripheral blood progenitor cell collections in 692 patients after the administration of myeloablative chemotherapy.* Blood 1995;**86**:3961-69.
5. Elliott C, Samson D, Armitage S, Lyttelton MP, McGuigan D, Hargreaves R, et al. *When to harvest peripheral-blood stem cells after mobilization therapy : prediction of CD34-positive cell yield by preceding day CD34-positive concentration in peripheral blood.* J Clin Oncol 1996;**14**:970-3.
6. Bensinger W, Appelbaum F, Rowley S, Storb S, Sanders S, Lilleby K, et al. *Factors that influence collection and engraftment of autologous peripheral-blood stem cells.* J Clin Oncol 1995;**13**:2547-55.
7. Pavone V, Gaydio F, Console G, Vitolo U, Iacopino P, Guarini A, et al. *Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell*

transplantation. Bone Marrow Transplant 2006;**37**:719-24.

8. Gorden LN. Sugrue MW, Lynch JW, Willians KD, Khan SA, Wingard JR, Moreb JS. *Poor Mobilization of Peripheral Blood Stem Cells is a Risk Factor for Worse Outcome in Lymphoma Patients Undergoing Autologous Stem Cell Transplantation.* Leuk Lymphoma 2003;**44**(5):815 - 20.
9. Kazuma I, Teruhiko K and Mine H., *Factors for PBSC collection efficiency and collection predictors.* Transf Aphere Sci 2004;**31**: 245-59.
10. Gandhi MK, Jestice K, Scott MA, Bloxham D, Bass G and Marcus RE. *The minimum CD34 threshold depends on prior chemotherapy in autologous peripheral blood stem cell recipients.* Bone Marrow Transplant 1999; **23**(1):9-13.
11. Moskowitz CH, Glassman J, Wuest D, Maslak P, Reich L, Gucciardo A, et al. *Factors affecting mobilization of peripheral blood progenitor cells in patients with lymphoma.* Clin Cancer Res 1998;**4**: 311–6.
12. Ketterer N, Salles G, Moullet I, Dumontet C, ElJaafari-Corbin A, Tremisi P, et al. *Factors associated with successful mobilisation of peripheral blood progenitor cells in 200 patients with lymphoid malignancies.* Br J Haematol 1998;**103**:235–42.
13. Daniel C, Vladimir K and Pavel J. *Factors affecting PBSC mobilization and collection in healthy donors.* Transf Aphere Sci 2005;**33(**3):275-83.
14. Massimo M, Ida C, Antonia C, Antonella D, Giuseppe I, Daniela M, et al. *Predictive factors that affect the mobilization of CD34+cells in healthy donors treated with recombinant granulocyte colony-stimulating factor (G-CSF).* J Clin Apher 2006;**21**(3):169-75.
15. Marcus RE and Huehns E. *Transfusional iron overload.* Clini Lab Hematol 1985;**7**:195–212.
16. Evens AM, Mehta J and Gorden LI. *Rust and corrosion in*

hematopoietic stem cell transplantation: the problem of iron and oxidative stress. Bone Marrow Transplant 2004;**34**(7):561-71.

17. Jillian O and Lawrie P. *Clinical Aspects of Hemochromatosis.* Semin Liver Dis 2005;**25**:381-91.
18. Cunningham RS, Giardina PJ, Grady RW, Califano C, McKenzie P and De Sousa M. *Effect of transfusional iron overload on immune response.* J Infect Dis 2000;**182**(Suppl1):S115-21.
19. Armand P, Kim HT, Cutler CS, Ho VT, Koreth J, Alyea EP, et al. *Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation.* Blood 2007;**109**(10):4586-8.
20. Altes A, Remacha AF, Sureda A, Martino R, Briones J, Canals C, et al. *Iron overload might increase transplant-related mortality in haematopoietic stem cell transplantation.* Bone Marrow Transplant 2002; **29**(12):987-9.
21. Min YH, Lee ST, Kim JS, Jang JH, Suh HC, Kim HO, et al. *Transplantation of Peripheral Blood Stem Cells Mobilized by Intensified Consolidation and Granulocyte Colony- Stimulating Factor in Acute Leukemia.* Yonsei Med J 2001;**42**(1):65-73.
22. Clyde DF, Jay G, Jeffrey A, Diana H and Finn BP. *Good and poor mobilizing patients differ in mobilized CD34+ cell adhesion molecule profiles.* Transfusion 2004;**44**(12):1769–73.
23. Clyde DF, Jay G, Jeffrey A, Diana H and Finn BP. *CD34+ cell adhesion molecule profiles differ between patients mobilized with granulocyte–colony-stimulating factor alone and chemotherapy followed by granulocyte–colony-stimulating factor.* Transfusion 2006;**46**(2):193–8.
24. Kim HK, Maria DLLS, Cassin KW, Virginia G and Giovanna T. *G-CSF down-regulation of CXCR4 expression identified as a mechanism for*

mobilization of myeloid cells. Blood 2006;**108**(3):812-20.

25. Bruno Nervi, Dan CL and John FD. *Cytokines and hematopoietic stem cell mobilization.* J Cell Biochem 2006;**99**(3):690-705.

26. Yuki N, Fumihito T, Kiyomi I, Hidetoshi Y, Mitsuo O, Goshi S and Yoshikazu M. *Soluble c-kit receptor mobilizes hematopoietic stem cells to peripheral blood in mice.* Exp Hematol 2004;**32**(4):390-6.

Abstract (In Korean)

혈액암 환자에서 말초혈액 조혈모세포 가동화와
혈청 ferritin 치와의 상관성 분석

<지도교수 민유홍>

연세대학교 대학원 의학과

박 인 혜

배경과 목적

혈액종양 환자들에 있어 반복적인 수혈로 인한 체내 철 과다는 흔히 볼 수 있는 부작용이다. 본 연구에서는 자가조혈모세포이식을 위해 시행하는 말초조혈모세포 가동에 있어 그 효율성이 체내 철 과다의 정도와 어떤 연관성을 가지는 지에 대해 살펴보았다.

연구 방법

말초조혈모세포 가동을 시행받은 총 51명의 혈액암 환자들을 대상으로 말초조혈모세포 모집술 전 혈청 ferritin, C-반응단백, 일반혈액검사, CD34 양성 세포를 측정하였으며 매 회 모집된 산물에서도 일반혈액검사, CD34 양성 세포를 측정하였다. 혈청 ferrtin과 조혈모세포가동율 사이의 연관성을 분석하기 위해 혈청 ferritin 값이 1,000ng/mL 이상이면서 수혈을 받은 병력이 있는 환자군을 고 ferritin 군으로 정의하였으며 1일 평균 모집된 CD34+ cell 수가 1.0x 10^6/kg 미만인 환자들을 비효율군으로 분류하여 효율군과 비교 분석하였다.

결과

비효율군과 효율군을 비교하였을 때 성별, 나이, 질병의 진행 정도,

질병의 골수 침범 여부, 조혈모세포 모집술 전 항암치료의 횟수, 모집술 첫째날 말초혈액에서의 백혈구 수에서는 차이가 없었다. 그러나 두 집단간에 누적 적혈구 수혈의 중앙값과 혈청 ferritin 값에서는 비효율군에서 유의하게 높게 나타났다. (각각 2 vs. 8 units, p=0.012 ; 1,670 ± 1,320 ng/mL vs. 965 ± 705 ng/mL, p=0.035). 1일 평균 모집된 CD34+ cells/kg 는 고 ferritin 군에서 저 ferritin 군에 비해 의미있게 낮았다. (2.0 ± 1.4 *vs.* 7.4 ± 5.8, p=0.001). 총 모집된 CD34+ cells/kg 역시 고 ferritin 군에서 통계적으로 유의하게 낮았으며 (5.5 ± 4.7 *vs.* 13.1 ± 9.1, p=0.01) 다변량 분석에서도 혈청 ferritin 값이 말초조혈모세포 가동율에 있어 독립적인 예측인자로서 유용할 수 있음을 알 수 있었다.

결론

본 연구를 통해서 반복적인 수혈로 인한 체내 철과다가 말초조혈모세포 가동에 있어 저해 요소로서 작용할 수 있음을 알 수 있었다. 따라서 자가조혈모세포 이식을 위한 말초조혈모세포 가동을 시행하기 전 철과다가 있는 환자들에 있어서는 철 킬레이트 치료가 고려되어야 할 것이다.

핵심 되는 말 : 수혈, 철 과다, 혈청 ferritin, 조혈모세포 가동