## References

1. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. Nat Rev Cancer 2002;2:175-87.
2. Iida S, Ueda R. Multistep tumorigenesis of multiple myeloma: its molecular delineation. Int J Hematol 2003;77:207-12.
3. Moreau P, Facon T, Leleu X, Morineau N, Huyghe P, Harousseau JL, et al. Recurrent 14q32 translocations determine the prognosis of multiple myeloma, especially in patients receiving intensive chemotherapy. Blood 2002;100:1579-83.
4. Fonseca R, Blood E, Rue M, Harrington D, Oken MM, Kyle RA, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood 2003;101:4569-75.
5. Soverini S, Cavo M, Cellini C, Terragna C, Zamagni E, Ruggeri D, et al. Cyclin D1 overexpression is a favorable prognostic variable for newly diagnosed multiple myeloma patients treated with high-dose chemotherapy and single or double autologous transplantation. Blood 2003;102:1588-94.
6. Miura K, Iida S, Hanamura I, Kato M, Banno S, Ishida T, et al. Frequent occurrence of CCND1 deregulation in patients with early stage of plasma cell dyscrasia. Cancer Science 2003;94:1-5.
7. Chesi M, Nardini E, Lim RS, Smith KD, Kuehl WM, Bergsagel PL. The t(4;14) translocation in myeloma dysregulates both FGFR3 and a novel gene, MMSET, resulting in IgH/MMSET hybrid transcripts. Blood 1998;92:3025-34.
8. Neri A, Murphy JP, Cro L, Ferrero D, Tarella C, Baldini L, et al. Ras oncogene mutation in multiple myeloma. J Exp Med 1989; 170:1715-25.
9. Santra M, Zhan F, Tian E, Barlogie B, Shaughnessy J Jr. A subset of multiple myeloma harboring the t(4;14)(p16;q32) translocation lacks FGFR3 expression but maintains an IGH/MMSET fusion transcript. Blood 2003;101:2374-6.
10. Hurt EM, Wiestner A, Rosenwald A, Shaffer AL, Campo E, Grogan T, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. Cancer Cell 2004;5:191-9.


*Multiple Myeloma*

## Double versus single autotransplantation in multiple myeloma; a single center experience of 100 patients


**One hundred patients with newly diagnosed multiple myeloma (MM) were treated with high-dose chemotherapy followed by single or double autologous stem cell transplantation (ASCT). Up-front treatment with a double ASCT tended to prolong progression-free and overall survival.**



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High dose therapy (HDT) and autologous stem cells transplantation (ASCT) are superior to conventional chemotherapy in multiple myeloma (MM),[1] and double autografting may be even better.[2] A total of 100 consecutive patients with newly diagnosed MM were treated with HDT and ASCT between 2/1992 and 3/2003: 73 patients (upper age limit 70 years) received a single and 27 patients (<61 years; 4 older patients) received a double translant (Table 1). Informed consent was obtained, and the double ASCT protocol was approved by the local Ethics Committee. After initial debulking therapy, usually 3-4 cycles of VAD, stem cells were mobilized with 2-4 g/m$^2$ of cyclophosphamide + granulocyte colony-stimulating factor. Details of the HDT are shown in Table 1. All patients received a blood graft. The EBMT response criteria were used.[3] A very good partial response (VGPR) was included and was otherwise similar to complete response (CR) but serum/urine immunofixation was positive. Overall survival (OS) and progression-free survival (PFS) were calculated from the first transplant to death.

**Table 1.** Patients' characteristics.

| | *Single ASCT* | *Double ASCT* |
|---|---|---|
| Age; years, median (range) | 59 (37-73) | 55 (45-66)[1] |
| Sex (female/male) | 32/41 | 12/15 |
| Myeloma type | | |
| IgG | 42 (58%) | 14 (52%) |
| IgA | 12 (16%) | 1 (4%) |
| IgD | 1 (1.3%) | 0 |
| Light chain | 16 (22%) | 11 (40%) |
| Plasmacytoma | 1 (1.3%) | 1 (4%) |
| Nonsecretory | 1 (1.3%) | 0 |
| Stage I/II/III | 7/37/29 | 2/10/15 |
| B2microglobulin >4 mg/L | 18 (38%)[2] | 5 (26%)[3] |
| Treatment line I/II/III | 54/16/3 | 22/2/3 |
| Local radiation therapy | 7 (9%) | 3 (11%) |
| T from onset Ther to Tx I; months, median (range) | 6 (3-12.5) | 5 (3-11) |
| T from onset Ther to Tx II; months, median (range) | | 11 (6-18) |
| HDT: Melphalan 140 mg/m$^2$ + TBI 12 Gy | 20 (27 %) | 1 (2 %) |
| Melphalan 200 mg/m$^2$ | 54 (73 %) | 53 (98 %)[4] |
| Interferon (IFN) maintenance therapy | 42 (57 %) | 11 (41 %) |
| Duration of IFN therapy; months, median (range) | 11 (1-101) | 16 (2-45) |

*[1]4 patients of more than 60 years of age: [2]not available for 27 patients; [3]not available for 8 patients: [4]total number of HDT (incl. 1st and 2nd transplants) in the double ASCT group.*

HDT supported by both the single and double ASCT was well tolerated. There was only one transplant-related death in the single transplant group. Organ-specific toxicities and engraftment kinetics were comparable between the first and second transplant procedures in the double ASCT group. The rate of good responses (CR + VGPR) increased from 18 to 71% (CR rate from 4 to 41%) with the single ASCT, and from 7 to 70% (CR rate from 0 to 52%) with the double ASCT. All patients responded to double autografting whereas there were three patients (4%) in the single ASCT group who did not. The median follow-up time from HDT is 51 (4-138) months in the single ASCT group and 46 (10-78) months in the double transplant group. For these groups, the median PFS was 29 (0-112) and 72+ (5-75) months ($p$=0.098), and the median OS 60 (0-138) and 78+ (10-78) months ($p$=0.078), respectively (Figure 1).

This non-randomized comparison between single and double autotransplantation as an up-front treatment of patients with MM shows that double autografting tends to

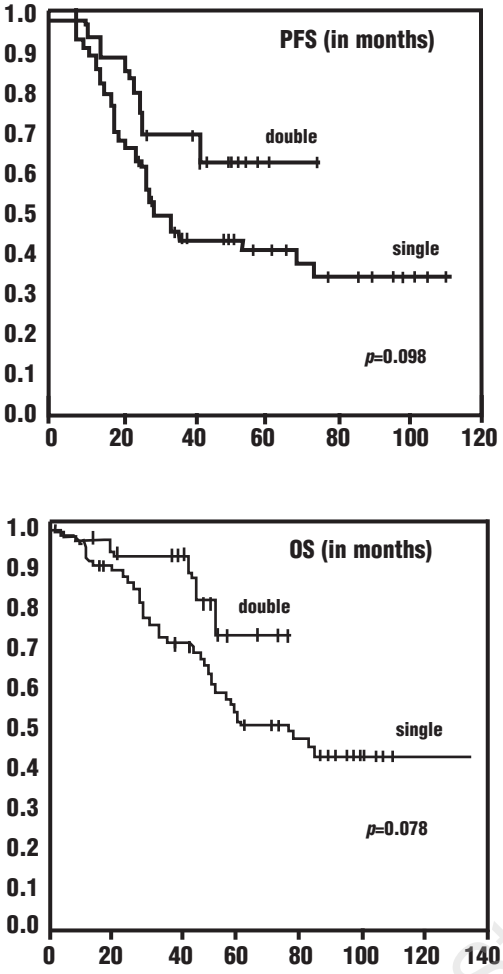


Figure 1. Progression-free survival and overall survival of patients receiving a single or double autograft.

prolong PFS and OS. A larger number of patients in the double-transplant arm might have made the difference statistically stronger. The difference between the groups could already be seen from the first year post-transplant. The reasons for not proceeding to a double transplant protocol in patients of less than 61 years revealed no major selection bias: patient´s own wish (9 patients), and insufficient amount of stem cells (3 patients). Age had no significant impact: PFS and OS curves only for patients under 61 years old also diverged in favor of double transplantation.

Achieving CR is the target of the initial therapy. For this purpose HDT with autografting is superior to conventional therapy, and double autografting may further improve the CR rate. The reported CR rates (immunofixation negative) after double autografting have varied from 30% to 55%,[4-6] and our observations are consistent with these figures. Our survival figures are in agreement with the results of the French randomized IFM94 study in which, however, the significant OS difference in favor of double transplantation emerged only after four years.[7] One apparent explanation for the longer survival in our study than in the French study is that our analyses were not performed by the intention-to-treat principle. Another explanation could be the lower proportion of stage III patients in our study. In contrast to the French IFM94 study there are some other ongoing randomized studies in which no difference in outcome between patients with single or double transplants has been found, but the follow-up is shorter than in the IFM94 Study.[2] Double autografting has resulted in a median event-free survival of 30 to 43 months[4,5,7] and OS of 58 to 68 months,[4,7] and a third of patients may live for 10 years.[8] Total body irradiation is not beneficial in the conditioning regimen[8,9] and, accordingly, we changed our HDT policy during the study period. The optimal timing of the second transplant is still an open question, i.e. whether to use it up-front or later as a rescue treatment.[10] Since double autografting is safe and well tolerated, patients up to the age of 65 to 70 years can undergo the procedure.[4,6] Further randomized protocols are needed to clarify the role of double autografting in multiple myeloma.

*Mervi Putkonen,* Auvo Rauhala,° Maija Itälä,* Marjut Kauppila,* Tarja-Terttu Pelliniemi,# Kari Remes**

*Departments of Internal Medicine* and Hematological Laboratory,# Turku University Central Hospital, Turku, and Department of Internal Medicine,° Vaasa Central Hospital, Vaasa, Finland*

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*Correspondence: Mervi Putkonen, M.D., Turku University Central Hospital, Dept. of Medicine, PL 52, 20521 Turku, Finland. Phone: international +358.2.3130000. Fax: international +358.2.3133043. E-mail: mervi.putkonen@tyks.fi*

## References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335:91-7.
2. Harousseau JL, Attal M. High-dose therapy in multiple myeloma. The Hematology J 2003;4:163-70.
3. Blade J, Samson D, Reece D, Apperley J, Björkstrand B, Garthon G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated with high-dose therapy and haematopoietic stem cell transplantation. Br J Haematol 1998;102:1115-23.
4. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood 1999;93:66-75.
5. Lemoli RM, Martinelli G, Zamagni E, Motta M, Rizzi S, Terragna C, et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy. Blood 2000;95:2234-9.
6. Weaver CH, Zhen B, Schwartzberg LS, Leff R, Magee M, Geier L, et al. Phase I-III evaluation of rapid sequence tandem high-dose melphalan with peripheral blood stem cell support in patients with multiple myeloma. Bone Marrow Transplant 1998;22:245-51.
7. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-502.
8. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg /m2 as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma. Final analysis of the IFM 95-02 randomised trial. Blood 2002;99:731-5.
9. Harousseau JL, Attal M, Divine M, Marit G, Leblond V, Stoppa AM, et al. Autologous stem cell transplantation after first remission induction treatment in multiple myeloma: a report of the French Registry on autologous transplantation in multiple myeloma. Blood 1995;85:3077-85.
10. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger A, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment ? Results of multicenter sequential randomized clinical trial. Blood 1998;92:3131-6.