行政院國家科學委員會補助專題研究計畫成果報告

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※ 合併運用 mafosfamide 處理後之自體骨髓及週邊幹細 ※
※ 細胞移植做為成人急性骨髓性白血病之鞏固治療之 ※
※ 研究 ※
※ ※
※Autotransplantation using combination of mafos-famide ※
※purged bone marrow and peripheral blood stem cell as ※
※consolidation of patient with acute myeloblastic leukemia※
※ in remission. ※
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執行期間：89 年 03 月 01 日至 90 年 06 月 30 日

計畫主持人：陳耀昌

共同主持人：姚明

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□赴國外出差或研習心得報告一份

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□出席國際學術會議心得報告及發表之論文各一份

□國際合作研究計畫國外研究報告書一份

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一、中文摘要

為了加速對成人急性骨髓性白血病患者接受自體造血幹細胞移植後造血系統之恢復及降低白血病復發率因此，我們和法國團隊(Leader: N.C. Gorin 教授，Paris, France)，合作進行「用 mafosfamide 處理過之自體骨髓移植及週邊幹細胞移植做為 AML 病人之鞏固治療」之一項 Phase II 的專題研究計劃研究。共有三位病患進入此項治療計畫。初期結果顯示本計劃可有效加速病患在接受自體造血幹細胞移植後造血系統之恢復。然而對復發率是否降低則仍有待觀察。

關鍵詞：自體造血幹細胞移植, 急性骨髓性白血病

Abstract

In order to accelerated the hematopoietic recovery and reducing the relapse rate in acute myeloblastic leukemia (AML) patients receiving autologous hematopoietic stem cell transplantation (AHSCT). With the cooperation with French group (coordinator: professor N.C. GORIN), we had successfully conducted the protocol of autotransplantation using combination of mafosfamide-purged bone marrow (BM) and peripheral blood stem cell (PBSC) as consolidation of patient with AML. The preliminary results showed this strategy might be beneficial for some AML patients.

Keywords: acute myeloblastic leukemia, autologous hematopoietic stem cell transplantation, mafosfamide

二、 計畫緣由與目的

For accelerating the hematopoietic recovery and reducing the relapse rate in acute myelogenous leukemia (AML) patients receiving autologous hematopoietic stem cell transplantation (AHSCT). With the cooperation with French group (coordinator: professor N.C. GORIN, Hôpital Saint-Antoine, Paris, France), we conducted a pilot phase II study of autotransplantation using combination of mafosfamide- purged bone marrow (BM) and peripheral blood stem cell (PBSC) as consolidation of patient with AML in remission. The aims of this protocol are: 1) increase the quantity of healthy

hematopoietic progenitors administered to patients receiving autotransplantation of mafosfamide-purged BM, by adding mafosfamide-purged PBSC. 2) study of the impact of this increment of HSCs dose, for engraftment kinetics and patient's survival. 4) compare the content of BM & PBSC submitted to mafosfamide purging procedure.

三、結果與討論

Though national science council had approved the protocol in March 2000, it passed the ethical committee in national health ministry in June 2000. So we started the processing for importing the Mafosfamide since July 2000. We finally got the Mafosfamide from ASTA pharmaceutics, Frankfort, Germany in September 2000. So we began to set up the standard procedure for mafosfamide in vitro purging of HSC autograft and quantitation of long-term culture initiating cell (LTC-IC) since September 2000.

From September 2000 to December 2001, three patients in National Taiwan University Hospital were enrolled in this protocol. All of them were belonged to high-risk group. The characteristics of these three patients were shown in Table 1. They were in the status of first complete remission during AHSC collection, but two of them were found in early relapse just before AHSCT.

Table1. Characteristics of patients

UPN	1	2	3
FAB Subtype	M4	M2	M1
Cytogenetics abnormalities	No	-18	No
Age	18	17	37
Sex	m	m	m
Hyperleukocytosis	+	-	+
Status during HSCT collection	CR1	CR1	CR1
Pre-AHSCT status	ER1	ER1	CR1

CR1:first complete remission;
ER1:first early relapse; m: male

Both PBSC and BM autografts were treated in vitro with mafosfamide and then cryopreserved. The HSC quantities of the autografts were measured by amount of total nucleated cell, CD34 positive cell, CFU-GM and LTC-IC. The data were shown in Table 2. The primitive HSC (LTC-IC) was more preserved than committed progenitor (CFU-GM) after mafosfamide treatment in both PBSC and BM autograft as our observation in previous study (Ref. 3)

Then they all received total body irradiation (TBI 1200 cGy) and high dose cyclophosphamide (60mg/Kg/ day for 2 days) as preparing regimen for autotransplantation. The post autoHSCT hematopoietic engraftment kinetics and follow up data were shown in table 3.

Table 2. HSC quantitation in autograft in pre- and post- mafosfamide purging procedure

A. PBSC

UPN	1	2	3
TNC*10^8/Kg			
Pre-P	3.22	3.19	1.69
Post-P	3.08	2.94	1.55
Recovery	97.6%	92.3%	91.7%
CD34+¢*10^6/Kg			
Pre-P	5.71	0.89	1.22
Post-P	3.76	0.88	1.04
Recovery	68.9%	98.9%	85.3%
CFU-GM*10^4/Kg			
Pre-P	22.87	4.81	13.64
Post-P	8.37	0.82	4.65
Recovery	36.6%	17.0%	34.1%
LTC-IC*10^3/Kg			
Pre-P	2.94	23.36	2.51
Post-P	1.29	12.24	1.37
Recovery	43.9%	52.4%	54.6%

B. BM

UPN	1	2	3
TNC*10^8/Kg			
Pre-P	4.52	2.17	1.32
Post-P	4.38	1.80	1.24
Recovery	96.9%	82.8%	94.2%
CD34+¢*10^6/Kg			
Pre-P	3.22	66.54	1.35
Post-P	2.98	55.98	1.01
Recovery	92.5%	84.1%	74.8%
CFU-GM*10^4/Kg			
Pre-P	9.51	12.91	10.64
Post-P	1.02	3.46	2.51
Recovery	10.5%	26.8%	23.6%
LTC-IC*10^3/Kg			
Pre-P	3.71	16.57	5.81
Post-P	3.05	9.55	4.14
Recovery	82.2%	57.6%	71.3%

CD34+¢:CD34 positive cells; CFU- GM: colony forming unit- granulocyte, monocyte; Pre-P: pre-mafosfamide purging procedure; Post-P:post mafosfamide purging procedure; TNC: total nucleated cells

Table 3. Post AHSCT engraftment kinetics and survival

UPN	1	2	3
ANC>500/uL	D12	D22	D14
ANC>1000/uL	D13	D28	D23
PLT>20K/uL	D13	D28	D23
PLT>50K/uL	D19	NY	NY
Post AHSCT Relapse Free Interval	6 M	NA	NA
Post AHSCT follow up period	12M	66D	30D

D:days; M:months; NY: not yet
NA: not applicable

Patients 1 and 2 did not receive G-CSF administration after HSC transfusion. Patient 3 received G-CSF injection post AHSCT due to borderline HSC content in autograft. The speed of engraftment was faster than ABMT only (Ref. 3). Because the case number was too low and follow up period was too short, the relapse rate can not be counted at present.

四、計畫成果自評

We had successfully conducted autotransplantation using combination of mafosfamide-purged bone marrow (BM) and peripheral blood stem cell (PBSC) as consolidation high-dose therapy of patient with AML. The preliminary results showed this strategy is safe and might be beneficial for some AML patients. The enrolled patient number was very small because there are several alternative treatments for this category of patients, and also because the entering criteria of the patients is very restrictive. Therefore, even our cooperative teams in whole France collected no more than 20 patients in total. Although it is not feasible to achieve statistical significance of our own series, our results will play an important part in the final report of this international collaborative study. The whole results of this international pilot study will be reported in annual meeting of American Society of Hematology (ASH) in year 2002 and will be submitted to *Blood* journal for publication.

五、參考文獻

1. Gorin NC: Autologous stem cell transplantation in acute myelocytic leukemia. *Blood 92, 1073-90, 1998*

2. Yao M, Bouchet S, Harnois C, Giarratana MC, Laporte JP, Gorin NC, Lopez M, Douay L. Quantitative and qualitative alterations of long-term culture- initiating cells in patients with acute leukaemia in complete remission. *British Journal of Haematology. 103:124-128,1998*

3. Laporte JP, Douay L, Lopez M, Labopin M, Jouet JP, Lesage S, Stachowiak J, Fouillard L, Isnard F, Noel-Walter MP, Pene F, Deloux J, Van Den Akker J, Grande M, Bauters F, Najman A, Gorin NC: One hundred twenty five adult patients with primary acute leukemia autografted with marrow purged by mafosfamide. A 10 year single institution experience. *Blood 84:3810, 1994*