

*Full Length Research Paper*

# Treatment of recurrent refractory mantle cell lymphoma by thalidomide in combination with interferon

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**Mantle cell lymphoma (MCL) is a highly aggressive non-Hodgkin's lymphoma with poor prognosis. This study aims to explore a new, safe approach for patients with recurrent refractory MCL. A total of six patients with recurrent refractory MCL were recruited. They all accepted thalidomide tablets (100 mg/day) orally every night, accompanied with interferon  $\alpha$ -2b (3 million units, injected subcutaneously) every other day. The patients were followed up for 41, 25, 20, 30, 40 and 36 months, respectively, with a median follow-up time of 33 months (20 to 41 months). No severe adverse reactions occurred. For patients with recurrent refractory MCL, the combination of thalidomide and interferon  $\alpha$ -2b showed a positive result to provide them a longer survival period with higher quality of life.**

**Key words:** Recurrent refractory mantle cell lymphoma, thalidomide, interferon  $\alpha$ -2b, combination, adverse reaction.

## INTRODUCTION

Mantle cell lymphoma (MCL) possesses the characteristics of poor response to chemotherapy, like indolent lymphoma, and the characteristics of short paracmasia, easy resistance and easy recurrence, like aggressive lymphoma. Therefore, MCL is a kind of B-cell lymphoma with unique biological characteristics and treatment response. Although, with the applications of the targeted drug-CD20 monoclonal antibody and bortezomib, and the improvements of radiotherapy, chemotherapy and hematopoietic stem cell transplantation, the remission rate has increased, the overall survival (OS) rate still could not be significantly improved. So, it would be of great significance to explore new, safe and effective treatment method. In this report, thalidomide was applied, accompanied with interferon (IFN), in the treatment of 6 patients with recurrent

refractory MCL and a good results was achieved.

## METARIALS AND METHODS

### Clinical data

Six patients with recurrent refractory MCL were admitted in the department of Hematology from March, 2010 to April, 2013, including 5 males and 1 female, aged 49 to 65 years old with the median age as 61.5. Patients provided us with signed informed consent in accordance with the declaration of Helsinki.

The different degrees of lymph node impingement in bilateral neck, armpits, groin and retroperitoneum appeared in 6 patients, among whom, patients also had bone marrow impingement and, 2 patients had intestinal and mesenteric lymph node impingement. Three patients also had B symptoms. These 6 patients had been diagnosed firmly by clinical, haemogram, bone marrow picture,

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**Table 1.** Detailed info of 6 patients with recurrent refractory MCL.

S/N	Gender/Age	Pathological typing	Staging and impingement sites	Bone marrow	Chromosome Karyotype	Treatment before	Results
1	M/62	MCL	IVA (rectum)	normal	normal	CHOP3 invalid	reached CR in 2 months
2	M/49	MCL	IIIA	normal	normal	RCHOP4+CHOP2, reoccurred at the 5 <sup>th</sup> month	reached PR in 1 month
3	M/56	MCL	III A	normal	normal	CHOP2 invalid	reached CR in 2 months
4	F/61	MCL	IVB (right colon)	normal	normal	2CHOP invalid	reached CR in 3 months
5	M/65	MCL	IVB (bone marrow)	mature lymphocyte 93.5%	45XY, t(11, 14), (q13; q32)	2CHOP, 2FC	reached PR in 2 months
6	M/64	MCL	IVB (bone marrow)	immature lymphocyte 22%, mature lymphocyte 62%	45XY, t(11, 14), (q13; q32)	1CHOP+Lasp, 1Hyper-CVAD B-CR	reoccurred after maintained CR for 10 months

cytogenetics and immunohistochemical staining. The conventional chemotherapy was invalid towards them, or the patients reoccurred after multiple chemotherapy. The details of the patients are shown in Table 1.

#### Diagnostic method

##### Immunohistochemical staining

After the biopsy, the tissues were fixed in 10% neutral formalin, then made normal paraffin-embedded sections with 4  $\mu\text{m}$  in thickness and stained with conventional hematoxylin-eosin. CD5, CD10, CD23, CD20, CD79a, CD30, CD43, CD56, Ki-67 and Cyclin D1 antibodies were used for the labeling. The above antibodies were all purchased from Dako CO., Ltd.

##### Cytogenetics

Bone marrow fluid used heparin for the anticoagulation, after the counting, inoculated in 5 ml RPMI1640 culture medium containing 20% fetal calf serum for 24 h at the concentration of  $2 \times 10^6 \text{ ml}^{-1}$ , then the products underwent Chromosomes R Band coloration. The analysis of splitting stages of 20 metaphase cells was then performed, and this described the chromosome karyotype according to the human cytogenetics, with the International Nomenclature (ISCN).

#### Conventional chemotherapy

The treatment programs are as follows: Rituximab,  $375 \text{ mg/m}^2$ ; CHOP scheme: CTX,  $750 \text{ mg/m}^2$ , ADM:  $50 \text{ mg/m}^2$ , VCR:  $1.4 \text{ mg/m}^2$ , PDN:  $100 \text{ mg/day}$ ; Lasp: 1 million units/day; FC scheme: FLU:  $25 \text{ mg/m}^2$ , CTX:  $300 \text{ mg/m}^2$ ; Hyper-CVAD B scheme: MTX:  $1 \text{ g/m}^2$ , Ara-C:  $3 \text{ g/m}^2$ .

#### Treatment of recurrence

Patients voluntarily accepted the thalidomide accompanied with IFN scheme: IFN  $\alpha$ -2b Injection (Wanfuyi, Shanghai Wanxing Bio-Pharmaceutical CO., Ltd.), 3 million units, injected subcutaneously, QOD, thalidomide tablets (Changzhou Pharmaceutical Factory CO., Ltd.)  $100 \text{ mg/day}$ . When the patients achieved a complete remission (CR) or partial remission (PR), the administration should be continued, with regular follow-up.

#### Effects evaluation and safety assessment

Patients were arranged with out-patient follow-up and inspection on a regular period, before and every 1 to 2 months after the treatment; blood routine examination, liver and kidney functions, electrolytes, color ultrasound, CT, bone marrow cell morphology and other tests such as ECG were performed. The efficacy was divided into CR, PR,

stable (SD) and progressive (PD) according to Cheson standards.

## RESULTS

### Efficacy

The patients were followed up for 41, 25, 20, 30, 40 and 36 months, respectively, with a median follow-up time of 33 months (20 to 41 months). Among the 4 patients, 3 of them were invalid when treated with CHOP scheme for 1 to 3 cycles, which gained CR after 2 to 3 months of the treatment, the disease-progressless survival period was 36 months and 18 months, respectively; 1 case showed the recurrent of a patient shortly after the application of RCHOP and obtaining CR, the disease-progressless survival period was 22 months. 1 case suffered the invalid effect with 2 cycles of CHOP, and still no markedly effect when replaced with 2 cycles of FC scheme. The scheme was applied for more than 2 months, the bone marrow mature lymphocyte ratio fell to 10%, and the systemic superficial lymph nodes significantly reduced than before, reaching PR. 1

case obtained CR after 1 cycle of CHOP+LASP scheme, then after the consolidation with 1 cycle COADB scheme and a cycle Hyper-CVAD B scheme, the patient suffered severe bi-lung infection due to bone marrow suppression, and had to stop the chemotherapy before applying the scheme intermittently for the therapy maintenance. In the 10th month, the bone marrow reexamination prompted that the patient underwent recurrence, which obtained remission with induction therapy again. The disease-progressless survival period was 10 months. The disease-progressless survival periods of the 6 patients were 36, 22, 18, 18, 3 and 10 months, respectively, with the median disease-progressless survival period as 18 months.

### Adverse reactions

Six (6) patients all suffered fever and leukopenia in the first 2 days; 4 cases had headache, fatigue and myalgia; 1 case had joint pain; 3 cases had constipation, and 1 patient had mild drowsiness. The above symptoms were all alleviated when given symptomatic treatment. No severe adverse reactions such as anaphylactic shock, deep vein thrombosis, bradycardia and other symptoms occurred. The combination of the two medicines showed no side effects.

### DISCUSSION

In 1994, D'Amato et al. (1994) reported that thalidomide would reduce the generation of vascular endothelial growth factor (VEGF), b-FGF and other angiogenic factors, thus changing the microenvironment of tumor growth. In 2006, the medicine was approved by FDA for the treatment of multiple myeloma, its single-agent application for the treatment of recurrent refractory MCL could reach the efficiency up to 30%.

With the in-depth study of the mechanism of thalidomide's anti-tumor effect, it was found that it did not only stimulate human CD8<sup>+</sup>T cells to release IL-2 and IFN, reducing the generation of cytotoxic IL-6 and IL-12 and oxidative DNA damage caused by free radicals (Richardson et al., 2002), but also indirectly improve the body's cytotoxic activity of NK cells and cytotoxic T cells through regulating the releasing of cytokine (Haslett et al., 1998; Davies et al., 2001). Recently, there were reports that showed thalidomide single-agent and/or combined with other drugs to treat recurrent refractory MCL.

Wilson et al. (2002), reported that 1 MCL case, had been applied to chemotherapy with rituximab, which eventually got PR when applied with thalidomide amine 800 mg/dl, the disease-progressless survival period was 6 months. Damaj et al. (2003), also reported that 2 MCL cases suffered recurrence when treated with single thalidomide for autologous hematopoietic stem cell

transplantation, with disease-progressless survival periods as 19 and 12 months, respectively. Kaufmann et al. (2004), used thalidomide combined with rituximab to treat 16 patients with recurrent refractory MCL, including 1 recurrent case of non-myeloablative allogeneic hematopoietic stem cell transplantation, 2 recurrent cases of autologous hematopoietic stem cell transplantation and 3 cases ever applied with rituximab, among whom 5 cases achieved CR (31%), 8 cases achieved PR (50%), with the efficiency up to 81%. The median disease-progressless survival period was 20.4 months.

Lymphoma has a long history of being treated with interferon, while it is generally considered that the interferon has a certain effect on low-grade malignant lymphoma, while little benefit on aggressive lymphomas. Sacchi et al. (2004), applied IFN combined with rituximab to treat 64 patients with recurrent indolent lymphoma, and CR was 33%, OR was 70% and follow-up was 22 months, with a median time as 19 months. After that, Davis et al. (2000) used rituximab combined with IFN to treat 38 patients with recurrent or refractory low-grade malignant lymphoma, follicular lymphoma and B-cell non-Hodgkin's lymphoma, among which CR was 11%, PR was 34% and OS was 45%.

However, Armitage and Coiffier (2000) drew a different conclusion. He summarized the efficacy of 54 patients treated only with IFN for the recurrent refractory diffuse large cell lymphoma, with a median age as 54 years (19 to 76 years old), 54% were male. T-cell lymphoma was as high as 31%, the skin impingement accounted for 26%. 62% patients showed plasma LDH elevated, the original lesion of 29 patients was CR before the recurrence. The median follow-up was 28 months (12 to 78 months). The median OR survival period was 43 months, CR was up to 66% and PR reached 34%.

### Conclusion

Thalidomide, accompanied with IFN, was applied in the treatment of 6 patients with recurrent MCL, the disease-progressless survival periods were 36, 22, 18, 18, 3 and 10 months, respectively, with the median period as 18 months, among whom 4 cases reached CR (50%) and 1 case reached PR (33%). The median follow-up time was 33 months (20 to 41 months). Currently, there no report yet about the combination of thalidomide and IFN in the treatment of recurrent relapsed MCL and other types of lymphoma. This study preliminarily provide the evidence that thalidomide accompanied with IFN was a valuable treatment option for relapsed refractory MCL, which still needed to further expand the sample size. The mechanism of the combination might be related to blocking tumor angiogenesis, enhancing the immune anti-tumor function and anti-tumor cell proliferation, though the specific anti-tumor mechanism was still unclear.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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