

Follow-Up Study of Follicular Lymphoma (FL) Treated Using Clarithromycin: Intravenous Erythromycin Combined with Prednisolone Treatment is Effective for Refractory FL Accompanied with an Ocular Lesion

Klaritromisin Kullanılarak Tedavi Edilen Foliküler Lenfoma (FL) İzleme Çalışması: Prednisolon Tedavisi ile Kombine İntravenöz Eritromisin, Oküler Lezyon Eşliğinde Refrakter FL İçin Etkilidir

Masashi Ohe, Haruki Shida, Yoshihiro Kusunoki, Satoshi Jodo, Ken Furuya

¹Department of Internal Medicine, JCHO Hokkaido Hospital, Sapporo, Japan

ABSTRACT

A 44-year-old man who presented lymphadenopathy was diagnosed with follicular lymphoma (FL). He was treated with rituximab, cyclophosphamide (CPM), doxorubicin, vincristine, and prednisolone (PSL), which resulted in a stable disease. The patient's subsequent clinical course included partial remission and stable disease, each of which was treated by chemotherapy. At the third regrowth of the tumor, however, the patient was diagnosed with leukocytopenia and could not undergo further chemotherapy. Regression of his lymphadenopathy occurred following treatment with clarithromycin (CAM), which has anti-lymphoproliferative effects. CAM was continued with good outcome and then CAM was tentatively discontinued. Invasion of the lymphoma cells into the thoracic vertebrae occurred and was successfully treated by radiotherapy. Thereafter, he was successfully treated with CAM combined with PSL and CPM. At 57 years of age, he developed pancytopenia owing to therapy-related myelodysplastic syndrome; consequently, CPM was discontinued. Treatment with CAM combined with PSL was continued successfully. However, 15 months later, he complained of exophthalmos. Magnetic resonance imaging revealed a right orbital lesion. As an alternative to CAM combined with PSL, treatment with intravenous EM combined with PSL was used successfully. This case shows that treatment with intravenous EM combined with PSL may be effective in some cases of refractory FL.

Key Words: Follicular lymphoma, clarithromycin, erythromycin, prednisolone

Received: 08.03.2019

Accepted:09.04.2019

ORCID ID: M.O. 0000-0002-6684-6688

Address for Correspondence / Yazışma Adresi: Masashi Ohe, MD Department of Internal Medicine, JCHO Hokkaido Hospital 1-8-3-18 Nakanoshima, Toyohira-ku, Sapporo 062-8618, Japan E-mail: oektsp1218@sweet.ocn.ne.jp

©Telif Hakkı 2020 Gazi Üniversitesi Tıp Fakültesi - Makale metnine <http://medicaljournal.gazi.edu.tr/> web adresinden ulaşılabilir.

©Copyright 2020 by Gazi University Medical Faculty - Available on-line at web site <http://medicaljournal.gazi.edu.tr/>
doi:<http://dx.doi.org/10.12996/gmj.2020.20>

ÖZET

Lenfadenopati tanısı alan 44 yaşındaki erkek hastaya foliküler lenfoma (FL) tanısı kondu. Rituksimab, siklofosfamid (CPM), doksorubisin, vinkristin ve prednizolon (PSL) ile tedavi edildi, bu da stabil bir hastalık ile sonuçlandı. Hastanın sonraki klinik seyri, her biri kemoterapi ile tedavi edilen kısmi remisyon ve stabil hastalıkları içeriyordu. Bununla birlikte, tümörün üçüncü büyümesinde, hastaya lökositopeni teşhisi kondu ve daha fazla kemoterapi göremedi. Lenfadenopatisinin gerilemesi, anti-lenfoproliferatif etkileri olan klaritromisin (CAM) tedavisinin ardından meydana geldi. CAM iyi sonuçlarla devam etti ve sonra CAM geçici olarak kesildi. Lenfoma hücrelerinin torasik omurlara invazyonu meydana geldi ve radyoterapi ile başarılı bir şekilde tedavi edildi. Daha sonra, PSL ve CPM ile birlikte CAM ile başarılı bir şekilde tedavi edildi. 57 yaşında, tedaviyle ilişkili miyelodisplastik sendrom; sonuç olarak, CPM durduruldu. PSL ile kombine CAM ile tedavi başarıyla sürdürüldü. Ancak, 15 ay sonra, egzoftalmi şikayeti oldu. Manyetik rezonans görüntülemeye sağ orbital lezyon saptandı. PSL ile birleştirilmiş CAM'a bir alternatif olarak, PSL ile birleştirilmiş intravenöz EM ile tedavi başarıyla kullanılmıştır. Bu vaka, PSL ile birleştirilen intravenöz EM ile tedavinin, bazı refrakter FL vakalarında etkili olabileceğini göstermektedir.

Anahtar Sözcükler: Foliküler lenfoma, klaritromisin, eritromisin, prednizolon

Geliş Tarihi:03.08.2019 **Kabul Tarihi:** 04.09.2019

INTRODUCTION

Macrolides (MACs), such as clarithromycin (CAM), have anti-lymphoproliferative effects as well as anti-bacterial activity (1). Glucocorticoids (GCs) have also anti-lymphoproliferative effects (2). There have been several previous reports that malignant lymphoma, leukemia, and plasma cell disorder, could be successfully treated with CAM combined with GCs (3-5).

We have previously reported a case of follicular lymphoma treated using CAM (6). Herein, we report this case again, in which the patient was treated using CAM combined with prednisolone (PSL) and erythromycin (EM) combined with PSL.

CASE REPORT

A 44-year-old man who presented lymphadenopathy was diagnosed with follicular lymphoma (FL). He was treated with rituximab (RX), cyclophosphamide (CPM), doxorubicin, vincristine, and PSL, which resulted in a stable disease. The patient's subsequent clinical course included partial remission and stable disease with episodes of tumor regrowth, each of which was treated by chemotherapy. At the third regrowth of the tumor, however, the patient was diagnosed with leukocytopenia and could not undergo further chemotherapy. Regression of his lymphadenopathy occurred following treatment with CAM (800 mg/day), which has anti-lymphoproliferative effects (6). CAM was continued for 14 months with good outcome and then CAM was tentatively discontinued. Invasion of the lymphoma cells into the thoracic vertebrae occurred after 6 months and was successfully treated by radiotherapy. Thereafter, he was successfully treated with CAM (800 mg/day) combined with PSL (10 mg/day) and CPM (50 mg/day) for 4 years. At 57 years of age, he developed pancytopenia owing to therapy-related myelodysplastic syndrome (MDS); consequently, CPM was discontinued. Treatment with CAM combined with PSL was continued successfully. However, 15 months later, he complained of exophthalmos. Magnetic resonance imaging revealed a right orbital lesion (Figure 1A). Add-on treatment with RX was ineffective. As an alternative to CAM combined with PSL (10 mg/day), treatment with intravenous EM (0.5 g three times a day) combined with PSL (30 mg/day) was used successfully (Figure 1B). The PSL dosage was decreased gradually to 20 mg/day.



Figure 1A. Magnetic resonance imaging showing a right orbital lesion.

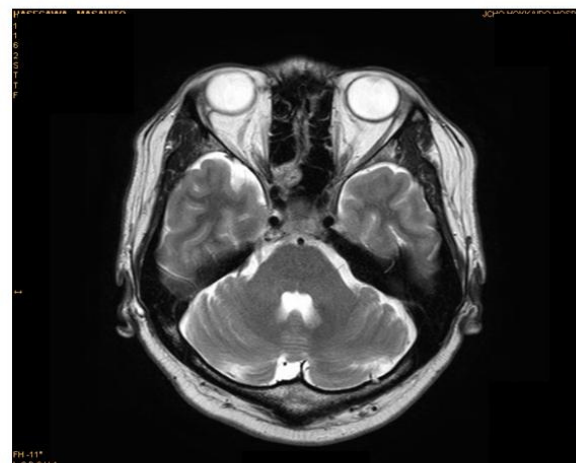


Figure 1B. Magnetic resonance imaging showing improvement of the right orbital lesion.

DISCUSSION

As stated above, MACs have recently been shown to exhibit anti-lymphoproliferative effects (1). Ishimatsu et al. reported two cases of pulmonary mucosa-associated lymphoid tissue lymphoma that were successfully treated using CAM (7). They speculated that CAM induced apoptosis of the lymphocytes by downregulation of the anti-apoptotic protein Bcl-xL. GCs are known to induce cell cycle arrest and apoptosis in lymphoid cells and are therefore an integral component in the treatment of lymphoid malignancies, particularly childhood acute lymphoblastic leukemia (8). Considering the apoptosis of lymphoid cells,

CAM combined with PSL may be beneficial in the treatment of lymphoproliferative diseases. In fact, we have reported a case of diffuse large

B-cell lymphoma successfully treated using CAM and PSL (3). Subsequently, we have reported a case of recurrent FL successfully treated using CAM combined with PSL and CPM (9). In the present case, the patient was treated with CAM, then CAM combined with PSL and CPM, and subsequently CAM combined with PSL. CAM combined with PSL and CPM regimen was considered to be the most effective treatment. However, this treatment induced therapy-related MDS. Thereafter, the patient was successfully treated with CAM combined with PSL. However, a right orbital lesion appeared 15 months later. Treatment with intravenous EM (0.5g three times a day) combined with PSL (30 mg/day) was effective. The reason why the intravenous EM combined with PSL treatment was more effective than CAM combined with PSL treatment might be partly because of the difference in PSL dosage between these two treatments.

CAM after oral administration has a rapid first-pass metabolism in the liver that results in absolute bioavailability levels of ~50% (10). We administered EM intravenously in order to elevate the absolute bioavailability level of the MAC.

EM was the first macrolide to be developed. New macrolides such as CAM and azithromycin have since been developed to supersede EM. CAM is a semisynthetic macrolide antibiotic, chemically identified as 6-O-methylerythromycin A (11). Only a slight structural change exists between CAM and EM. As a result, a close analogy exists between CAM and EM. In fact, EM as well as CAM has been reported to induce death of leukemic lymphoid cells (12). On the basis of these facts, the elevated absolute bioavailability of EM and/or above-mentioned slight structural change might be advantageous to intravenous EM combined with PSL treatment for providing anti-lymphoproliferative effects, as compared with CAM combined with PSL treatment.

More extensive research is required to validate our findings before intravenous EM combined with PSL treatment can be adopted on a wider basis.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Van Nuffel AM, Sukhatme V, Pantziarka P, Meheus L, Sukhatme VP, Bouche G. Repurposing Drugs in oncology (ReDO)—clarithromycin as an anti-cancer agent. *Ecanermedscience*. 2015;24:9:513. doi: 10.3332/ecancer.2015.513.
2. Lin KT, Wang LH. New dimension of glucocorticoids in cancer treatment. *Steroids* 2016;111:84-8.
3. Ohe M, Hashino S, Hattori A. Successful treatment of diffuse large B-cell lymphoma with clarithromycin and prednisolone. *Korean J Hematol* 2012; 47:293-7.
4. Ohe M, Hashino S. Successful treatment with clarithromycin for Mixed phenotype acute leukemia, T/myeloid, NOS. *Rinsho Ketsueki*. 2010;51:297-9.
5. Ohe M, Hashino S, Shida H, Horita T, Sugiura M. A case of Waldenstrom's macroglobulinemia treated using clarithromycin and prednisolone. *Transl Clin Pharmacol* 2017;25:134-7.
6. Ohe M, Hashino S. A case of follicular lymphoma treated using clarithromycin. *Korean J Hematol*. 2011; 46:203-6.
7. Ishimatsu Y, Mukae H, Matsumoto K, Harada T, Hara A, Hara S, et al. Two cases with pulmonary mucosa-associated lymphoid tissue lymphoma successfully treated with clarithromycin. *Chest*. 2010; 138:730-3.
8. Ploner C, Schmidt S, Presul E, Presul E, Renner K, Schrocksnadel K, et al. Glucocorticoid-induced apoptosis and glucocorticoid resistance in acute lymphoblastic leukemia. *J Steroid Biochem Mol Bio*. 2005; 93:153-60.
9. Ohe M, Hashino S. Successful treatment of recurrent follicular B-cell lymphoma with clarithromycin, prednisolone, and cyclophosphamide. *Korean J Intern Med* 2013; 28:377-9.
10. Chu SY, Deaton R, Cavanaugh J. Absolute bioavailability of clarithromycin after oral administration in humans. *Antimicrob Agents Chemother*. 1992. 36:1147-50.
11. Iwasaki H, Sugiura Y, Adachi T, Morimoto S, Watanabe Y. Structure of 6-O-methylerythromycin A (clarithromycin). *Acta Cryst* 1993;C49:1227-30.
12. Pillozzi S, Masselli M, Gasparoli L, D'Amico L, Polletta L, Veltroni M, et al. Macrolide antibiotics have an antileukemic effect by modulating the autophagic flux through the involvement of hERG1 potassium channels. *Blood Cancer J* 2016; 6:e42
1. Van Nuffel AM, Sukhatme V, Pantziarka P, Meheus L, Sukhatme VP, Bouche G. Repurposing Drugs in oncology (ReDO)—clarithromycin as an