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## ORIGINAL ARTICLE

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# Recent Advances in the Treatment of Lymphomas

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### ABSTRACT

*Malignant lymphoma is a common neoplasm and some are potentially curable if appropriate therapy is given. The use of the monoclonal anti-CD20 antibody rituximab in the management of follicular lymphoma has improved the outcome of patients. Rituximab and chemotherapy combination is now standard in the initial treatment of advanced-stage follicular lymphoma. Furthermore, rituximab maintenance therapy has also been shown to prolong progression-free survival in first clinical remission as well as in relapse following salvage therapy. In addition to rituximab, the use of purine analogue fludarabine in follicular lymphoma has also been shown to enhance the response rate. On the other hand, chemotherapy designed for the treatment of B-cell lymphoma is generally ineffective for NK/T-cell lymphoma, a highly malignant lymphoma that is prevalent in Asian countries. Recently, preliminary results from international study and our local centre have shown that the SMILE regimen (comprising dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) is very effective and would potentially improve the survival of patients with NK/T-cell lymphoma.*

**Key Words:** *Antibodies, monoclonal; Antineoplastic combined chemotherapy protocols; Lymphoma, extranodal NK-T-cell; Lymphoma, follicular; Prednisone; Vincristine*

## 中文摘要

### 淋巴瘤治療的最新發展

謝偉財、鄭沃林

惡性淋巴瘤是一種很常見的腫瘤，施以適當的治療可以治癒部分的患者。使用抗CD20單克隆抗體利妥昔單抗（rituximab）醫治濾泡性淋巴瘤有助改善病情。而rituximab結合化療已成為治療晚期濾泡性淋巴瘤的第一線標準治療方法。此外，利妥昔單抗維持治療已被證實可為病情得到首發性緩和，及經過搶救性治療的復發性濾泡性淋巴瘤病人延長無惡化生存期。除了利妥昔單抗，嘌呤類似物fludarabine也為濾泡性淋巴瘤患者加強療效。另一方面，專為B細胞淋巴瘤而設的化療通常對NK/T細胞淋巴瘤（一種多見於亞洲地區的高度惡性淋巴瘤）無效。國際及本地研究最近得出的初步結果均顯示SMILE方案（包括地塞米松、甲氨蝶呤、異環磷酰胺、左旋天冬醯胺酶及依托泊苷）對於NK/T細胞淋巴瘤患者很有效，並對改善病人的存活率有潛在價值。

### INTRODUCTION

Lymphoma is a common neoplasm worldwide. In Hong Kong, it is among the 10 most prevalent malignancies, with an increasing incidence in the past decade. Depending on the histological type, some lymphomas are potentially curable if optimal treatment is given. For

instance, the outcome of patients with B-cell lymphoma has been much improved with anti-CD20 monoclonal antibody (rituximab)-based therapy. On the other hand, conventional chemotherapy designed for B-cell lymphomas is not effective for NK/T-cell lymphoma, and new treatment protocol for this highly malignant

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tumour is needed. We shall initially discuss the impact of rituximab and the purine analogue fludarabine on the management of follicular lymphoma. Subsequently, the use of the new chemotherapy regimen SMILE in the treatment of NK/T-cell lymphoma will be discussed.

## **FOLLICULAR LYMPHOMA**

Follicular lymphoma is the second most common lymphoma, comprising approximately 15 to 20% of all mature-B-cell lymphomas, and about 40 to 50% of 'low-grade' lymphomas in Hong Kong. Follicular lymphoma is considered to be an indolent lymphoma and most patients survive for years. For early- or limited-stage disease, in selected patients the 'watch and wait' approach may be offered. Locoregional radiotherapy may also be applied. Conversely, for patients with advanced-stage disease, systemic chemotherapy is recommended. With the introduction of the anti-CD20 monoclonal antibody rituximab in the past several years, the treatment paradigm for follicular lymphoma has changed.<sup>1</sup>

### **Use of Rituximab and Fludarabine in the Treatment of Follicular Lymphoma**

Treatment of follicular lymphoma usually involves the use of alkylating agent-based chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristin, and prednisolone) or CVP (cyclophosphamide, vincristine, and prednisolone). Recent clinical trials have investigated the benefit of including rituximab in the treatment approach. A phase III study by Hiddemann et al<sup>2</sup> randomised patients with untreated, advanced-stage follicular lymphoma to receive either CHOP together with rituximab (R-CHOP) or CHOP alone. A significantly higher overall response rate, a longer duration of remission, and a better overall survival were observed in the R-CHOP group. Similarly, another phase III randomised trial investigated the combination of rituximab with CVP (R-CVP) for advanced-stage follicular lymphoma.<sup>3</sup> Patients receiving R-CVP had significantly better overall and complete response rates as compared to those receiving CVP only. At a median follow-up of 30 months, time to progression and time to treatment failure were both longer in the R-CVP arm. As a result of these encouraging results in the treatment of advanced-stage follicular lymphoma, the addition of rituximab to conventional chemotherapy is now the standard of care. Despite a high remission rate following rituximab-based chemotherapy, many patients still experience disease relapse. Therefore, maintenance therapy has been administered to improve

disease-free as well as overall survival. The role of rituximab in maintenance therapy was first established in patients with relapsed follicular lymphoma. A phase III randomised controlled trial has confirmed that rituximab maintenance (375 mg/m<sup>2</sup> every 3 months for a maximum of 2 years) improved progression-free survival in relapsed follicular lymphoma following CHOP or R-CHOP salvage therapy.<sup>4</sup> More recently, the benefit of rituximab maintenance after first-line rituximab-based chemotherapy has also been shown in the PRIMA (Primary RItuximab and MAintenance) study. At the 2-year follow up, progression-free survival in the rituximab maintenance group was 82%, compared with 66% in the observation arm.

In addition to therapy based on alkylating agents, the use of a purine analogue such as fludarabine has been explored in the treatment of follicular lymphoma. Zinzani et al<sup>5</sup> reported higher response rates when patients were treated with a combination of fludarabine and mitoxantrone as opposed to CHOP. The benefit of the sequential use of rituximab in patients treated with either fludarabine and mitoxantrone or CHOP was similar and no direct comparison was made in their study. Similarly, Hagenbeek et al<sup>6</sup> found that fludarabine alone was superior to CVP. Such improvements, however, did not translate into better progression-free or overall survival. In our centre, we have been using FND (fludarabine, mitoxantrone, and dexamethasone) for the treatment of grade 1-2 advanced-stage follicular lymphoma with encouraging results.<sup>7</sup> The overall response rate was 77.5% and complete remission rate of 48%. Median progression-free survival was around 25 months, which was comparable to other published data.

### **EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE**

Extranodal NK/T-cell lymphoma, nasal type is a distinct clinicopathological entity with a peculiar geographic distribution.<sup>8</sup> Although extremely rare in western populations, it constitutes about 4% of all lymphomas in Hong Kong. Most patients present with nasal or nasopharyngeal mass lesions, which ulcerate and give rise to perforation of nasal septum or hard palate. Local radiotherapy alone is not effective, as approximately 40% of such patients experience systemic relapses.<sup>8,9</sup> Treatment with chemotherapy is therefore essential to reduce the risk of systemic relapse. Owing to a lack of standard chemotherapy protocol for NK-cell malignancies, in the past oncologists frequently used the CHOP regimen as treatment but response was

unsatisfactory.<sup>8,9</sup> One possible explanation may be related to the high expression level of p-glycoprotein in NK lymphoma cells, which could confer multidrug resistance (MDR) phenotypes, rendering CHOP therapy ineffective.<sup>10</sup>

### **The SMILE Regimen and Treatment Protocol for NK/T-cell Lymphoma**

The SMILE regimen (comprising dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) was designed to address these limitations by incorporating non-MDR-dependent drugs, and the addition of L-asparaginase which has displayed single agent activity against NK cells in vitro.<sup>11</sup> In collaborating with other centres in the Asia Pacific, this regimen has been tested for treating patients with NK/T-cell lymphoma of all stages. Published findings from a phase I study have confirmed the effectiveness of the SMILE regimen in refractory and relapsed NK/T-cell lymphoma.<sup>12</sup> Currently in our centre, patients with stage I-II disease are treated with a total of 6 courses of SMILE chemotherapy and also involved field radiotherapy after the initial 3 courses. Our unpublished data showed that 100% of patients with stage I-II disease achieved a durable complete remission. For patients with advanced-stage disease, a total of 6 courses of SMILE chemotherapy are given. Allogeneic haematopoietic stem cell transplantation should be considered to maintain the remission. High-dose chemotherapy with autologous haematopoietic stem cell rescue does not appear to benefit patients with early-stage disease, and is ineffective for advanced-stage disease.<sup>13</sup> Therefore, it is not included as part of the treatment algorithm in our centre.

### **CONCLUSION**

Complementing standard treatments in follicular lymphoma, rituximab and fludarabine have improved remission rates and are currently used widely by haematologists and oncologists. In our centre, the use of the SMILE regimen in the treatment of NK/T-cell lymphoma has proven to be highly effective. With further upcoming data from the NK Tumor Study Group (Japan, Hong Kong, and Korea), the SMILE regimen

has the potential to become standard chemotherapy for NK/T-cell lymphoma.

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