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Clinical Observation of FMD Regimen: Fludarabine, Mitoxantrone, Dexamethasone, in Treatment of Non-Hodgkin's Lymphoma

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OBJECTIVE To evaluate the clinical effectivity and toxicity of the regimen FMD (fludarabine, mitoxantrone, dexamethasone) in patients with non-Hodgkin's lymphoma.
METHODS Thirty-two patients, twenty-four of whom had indolent B-cell lymphoma, 6 peripheral T-cell lymphoma, two diffuse large B-cell lymphoma, received FMD. Treatment comprised: fludarabine 25~30 mg/m^2 days 1~3, mitoxantrone 8~10 mg/m^2 day 1, and dexamethasone 20~30 mg /m^2 days 1~5. At the same time, patients received prophylaxis against conditional infection with trimethoprim-sulfamethoxazole, fluconazole, acyclovir and immunoglobulin.
RESULTS Of the thirty-two patients treated, the complete response (CR) rate, partial response (PR) rate and overall response (OR) rate were 56.3%, 21.9% and 78.2% respectively. The CR and OR rate of 24 patients with indolent B-cell lymphoma were 66.7% and 88.3% respectively. Two of six patients with peripheral T-cell lymphoma were of complete response type and one was of partial response type. One of two patients with diffuse large B-cell lymphoma was partial response. The dominating toxicity was myelotoxicity and immunotoxicity. There was no treatment associated death in all patients treated with FMD. Grade 3~4 neutropenia occurred in 43.8% patients, 12.5% patients had infections and 9.3% developed grade 3~4 thrombocytopenia. At a median follow-up of 24 (5~54) months, the 2-year overall-survival rate and progression-free survival rate were (87.5 ± 1.4)% and (83.3 ± 1.6)% respectively. The 2-year OS and PFS rates of the indolent group were (93.75 ± 6.25)% and (87.5 ± 8.54)%.
CONCLUSION FMD regimen was highly effective with low toxicity in the treatment of non-Hodgkin's lymphoma, especially in indolent B-cell lymphoma. It also helps to improve the prognosis even in some aggressive lymphoma, such as peripheral T cell lymphoma.

KEY WORDS: fludarabine, mitoxantrone, dexamethasone, lymphoma, non-Hodgkin's.

Introduction

Fludarabine, one of the purine analogues, is an effective antimetabolite with significant activity inhibiting synthesis of DNA, RNA and protein. Both as a single agent and in combination regimens, it has demonstrated great effects in the treatment of patients with non-Hodgkin's lymphoma (NHL), especially indolent NHL[1-6]. Fludarabine has been utilized for several years in China. This study was

conducted to evaluate the clinical efficacy and toxicity of FMD regimen in patients with non-Hodgkin's lymphoma.

Patients and Methods

Patients

During November 2002 to October 2007, 32 NHL patients were enrolled into this study, among which 17 were newly diagnosed and 15 were relapsed and refractory NHL patients. Eligibility criteria included: ECOG scores ≤ 2, normal liver, renal, heart and lung function. Clinical characteristics are shown in Table 1. All patients were diagnosed with determined histopathology and immunohistochemical stain or flow cytometry for cell surface antigen. Pathologic classification was decided according to WHO lymphatic tumor classification (2001). The study was approved by the institution's Research Ethics Committee and informed consent was obtained from all the patients.

Of the 32 cases, 19 were male and 13 were female, with a range of age from 33 to 78 years old (median 53 years). Twenty-four cases were indolent B lymphocytic NHL (7 chronic lymphocytic leukemia/small lymphocytic lymphom, 7 follicular cell lymphoma, 5 extranodal marginal zone B cell lymphoma MALT type, 3 lymphoplasmacytic lymphoma, 2 mantle cell lymphoma) and 8 were aggressive NHL (6 peripheral T cell lymphoma, 2 diffuse large B-cell lymphoma). There was no statistically significant difference in age, sex distribution, clinical stage and serum β2 microglobulin (β2-MG) level between the indolent group and aggressive group ($P > 0.05$). The difference of serum LDH level between the two groups was significant ($P < 0.001$, Table1).

Table 1. Patients' characteristics.

Patients' characteristics	Indolent	Aggressive	*P*
Newly diagnosed *vs.* refractory	14:10	3:5	> 0.05
Mean age (years)	53 (33~78)	57 (32~68)	> 0.05
Male *vs.* Female	14:10	6:2	> 0.05
Stage I~II *vs.* III~IV	8:16	1:7	> 0.05
Serum LDH (U/L)	221.8 ± 115	410.9 ± 112	< 0.001
Serum β2-MG (mg/L)	2.85 ± 1.42	2.97 ± 0.89	> 0.05

Treatment schedule

All patients received fludarabine (ScheringPharma, Nanjing, China) 25~30 mg/m^2 intravenously (i.v.) on days 1~3, mitoxantrone 8~10 mg/m^2 i.v. on day 1 and dexamethasone 20~30 mg/m^2 i.v. on days 1~5. Routine anti-emetics were given, usually ondansetron. Treatment was repeated every 28 days for 6 cycles. Treatment was delayed when the neutrophil count was less than 4.0 × 10^9/L or the platelet count less than 100 × 10^{12}/L or with infection. If blood count recovery was delayed by more than six weeks, the fludarabine and mitoxantrone doses were reduced by 25% for all subsequent cycles. In patients with kidney dysfunction (serum creatinine increased to twice the normal level), the dose would be adjusted according to creatinine clearance; if serum bilirubin exceeded twice the normal value that related to infiltration by lymphoma, the mitoxantrone dose was reduced by 50% and increased to full dose when bilirubin returned to normal. If repeated infection occurred during the course of treatment, or the condition progressed after two courses of treatment, or intolerable toxic reactions occurred during the treatment, the protocol would be terminated. All patients received prophylaxis against Pneumocystis carinii pneumonia (PCP) with trimethoprim-sulfamethoxazole (except for one allergic patient), fluconazole to avoid fungal infection, and aciclovir tablet to avoid virus infection. Most patients received support treatment with 5~10 g immunoglobulin for every 28 days.

Observation indexes

Blood routine, SGPT, SGOT, Bilirubin, blood sugar and Scr was examined before each cycle of chemotherapy. Responses defined by WHO were used throughout the study. Complete remission (CR) was defined as negative clinical symptom and examinations. Partial remission (PR) was defined as tumor size (maximum diameter × vertical diameter) shrinkage over 50%. Stable disease (SD) was tumor size decreased less than 50% or increased less than 25%. Progression of disease (PD) was defined as more than 25% increase of tumor size or the presence of new clinical symptoms. The adverse effect was evaluated according to WHO standards (I~IV).

Statistical analysis

The independence between two categorical was analyzed by χ^2 test and Student's *t* test. Survival rates were estimated by using the Kaplan-Meier method.

Results

Responses

Overall, 32 patients completed 133 cycles of treatments, and each patient was treated for more than 2 courses (mean 4.2 cycles). Among them, 56.3% patients achieved CR and 21.9% PR. The OR (overall remission) rate was 78.2%. Twenty-four patients with indolent NHL completed 105 cycles (mean 4.4 cycles), and 8 patients with aggressive NHL completed 28 cycles (mean 3.5 cycles). There was no statistically significant difference in CR rate (66.7% *vs.* 25%, $P > 0.05$) between those two groups, while OR rates are significantly different (88.3% *vs.* 50%, $0.01 < P < 0.05$, Table 2). There was no significant difference in CR rate (76.5% *vs.* 40%, $P > 0.05$) between newly diagnosed and the refractory/relapsed patients, while there was statistically significant difference in OR rate (94.1% *vs.* 53.3%, $0.01 < P < 0.05$, Table 3).

Table 2. Responses of indolent and aggressive NHL groups.

	Indolent	Aggressive	*P*
Evaluable (*n*)	24	8	-
CR (%)	66.7	25	> 0.05
OR (%)	88.3	50	0.01 < *P* < 0.05

Table 3. Responses of newly diagnosed and relapsed/refractory NHL groups.

	Newly diagnosed	Relapsed and refractory	*P*
Evaluable (*n*)	17	15	-
CR (%)	76.5	40	> 0.05
OR (%)	94.1	53.3	0.01 < *P* < 0.05

Adverse reactions

Hematological toxicity was the major toxicity (Table 4). Nine patients had grade 3~4 neutropenia and 4 of them developed respiratory infections. Meanwhile, grade 3-4 thrombocytopenia occurred in 3 patients. All the patients recovered after treatment with G-CSF, IL-11 and anti-infection drugs. Nonhematologic toxicities were mainly in the gastrointestinal system. Four patients still suffered from grade 1~2 nausea and vomiting despite ondansetron prophylaxis. Grade 1 renal dysfunction was found in one patient and grade 1 impaired liver function in another patient. There was no treatment associated death in all patients treated with FMD.

Table 4. Adverse reactions observed in 32 patients treated with FMD regimen.

Toxicity (grade 3~4)	Rate (%)
Neutropenia	28.1
Thrombocytopenia	9.4
Infection	12.5
Gastrointestinal reaction	12.5
Renal dysfuntion	3.1

Follow-up findings

The median follow-up of surviving patients was 24 months (a range of 5~54 months). The 2-year overall survival rate was (87.5 ± 1.4)%, and progress free survival (PFS) was (83.3 ± 1.6)%. The differences were significant between 2-year OS and PFS rates of the indolent and the aggressive group [(93.75 ± 6.25)% *vs.* (33.3 ± 21.1)%, (*P* = 0.009)], [(87.5±8.54)% *vs.* (33.3 ± 21.1)%, *P* = 0.025], respectively (Table 5). The difference was significant in the 2-year OS rates between the newly diagnosed and relapsed/refractory groups [100% *vs.* (55.6 ± 17.6)%, *P* = 0.021], but there was no statistically significant difference in 2-year PFS rates [(91.6± 8.7)% *vs.* (44.4±17.6)%, *P* = 0.119, Table 6].

Table 5. Two-year OS and PFS of indolent and aggressive NHL groups.

	Indolent	Aggressive	*P*
OS (%)	93.75 ± 6.25	33.3 ± 21.1	0.009
PFS (%)	87.5 ± 8.54	33.3 ± 21.1	0.025

Table 6. Two years OS and PFS of newly diagnosed and relapsed/refractory NHL groups.

	Newly diagnosed	Relapsed/refractory	*P*
OS (%)	100	55.6 ± 17.6	0.021
PFS (%)	91.6 ± 8.7	44.4 ± 17.6	0.119

Discussion

McLaughlin et al.[7] has reported the results of FMD regimen in 51 relapsed and refractory NHL patients in 1996, with the CR rate 47% and PR rate 47%. Bone marrow suppression and infection were the primary toxicity. Half of the infections proved to be opportunistic infection especially herpes Zoster and PCP. Since then, FMD regimen was the front-line choice for indolent NHL[8,9]. Tsimberidou et al.[10] reported 73 newly diagnosed indolent NHL patients treated with FMD, among whom the CR rate was 79%, OR 97% and 5 year OS rate 84%. FMD was also used in aggressive T cell lymphoma. Au et al.[11] reported 1 patient with Subcutaneous Panniculitis-like T Cell Lymphoma achieved CR after FMD treatment and remained CR 15 months after that. There were also some reports about FMD regimen for B cell indolent lymphoma and 1arge granular lymphocytes leukemia (LGLL). The CR and OR rate in B cell indolent lymphoma was 50.5% and 68.5%, and 56% and 67% in LGLL[12].

Fludarabine has been used in patients accepted in our hospital for about 5 years. Our data indicated that the OR rate and CR rate of FMD regimen are similar to those previously reported in B-cell indolent lymphoma[13,14]. A comparably high OR rate was observed in the newly diagnosed group when compared to the relapsed/refractory group though the difference of CR rates was not statistically significant. Besides, the results of FMD in 6 patients with peripheral T cell lymphoma were also encouraging, with two CR (one patient has survived without disease for 54 months), one PR and one SD. Among the two patients with refractory diffuse large B-cell lymphoma, one achieved PR and the other progressed. FMD was generally well tolerated. Bone marrow suppression and immunosuppression are the major toxicities. Tsimberidou et al.[15] reported that there was severe immunosuppression in patients treated with FMD, displaying low CD4 cell count and decreased IgG level. Grade 3~4 infection occurred in 19% of patients and prophylaxis against PCP was recommended. In our

study, grade 3~4 neutropenia occurred in 28.1% of the patients and 12.5% of the patients got infections. There is no opportunistic infection because of the prophylaxis against PCP and virus and support treatment with immunoglobulin.

In summary, our data showed that FMD regimen is effective and well tolerated in the treatment of NHL. The therapeutic effect is especially good in indolent B-cell lymphoma. It also helps to improve the prognosis even in some aggressive lymphoma, such as peripheral T cell lymphoma.

References

1 Hagenbeek A, Eghbali H, Monfardini S, et al. Phase III intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage III and IV low-grade malignant Non-Hodgkin's lymphoma. J Clin Oncol 2006; 24: 1590-1596.
2 Soubeyran P, Monnereau A, Eghbali H, et al. Fludarabine phosphate-CVP in patients over 60 years of age with advanced, low-grade and follicular lymphoma: a dose-finding study. Eur J Cancer 2005; 41: 2630-2636.
3 Rao R, Shammo JM, Enschede SH, et al. The combination of fludarabine, cyclophosphamide, and granulocyte-macrophage colony-stimulating factor in the treatment of patients with relapsed chronic lymphocytic leukemia and low-grade Non-Hodgkin's lymphoma. Clin Lymphoma 2005; 6: 26-30.
4 Foussard C, Colombat P, Maisonneuve H, et al. Long-term follow-up of a randomized trial of fludarabine-mitoxantrone, compared with cyclophosphamide, doxorubicin, vindesine, prednisone (CHVP), as first-line treatment of elderly patients with advanced, low-grade non-Hodgkin's lymphoma before the era of monoclonal antibodies. Ann Oncol 2005; 16: 466-472.
5 Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J Clin Oncol 2005; 23: 694-704.
6 Fabbri A, Lenoci M, Gozzetti A, et al. Low-dose oral fludarabine plus cyclophosphamide as first-line treatment in elderly patients with indolent non-Hodgkin lymphoma. Br J Haematol 2007; 139: 90-93.
7 McLaughlin P, Hagemeister FB, Romaguera JE, et al. Fludarabine, mitoxantrone, and dexamethasone: an effective new regimen for indolent lymphoma. J Clin Oncol 1996; 14: 1262-1268.
8 Bordonaro R, Petralia G, Restuccia N, et al. Fludarabine, mitoxantrone and dexamethasone as front-line therapy in elderly patients affected by newly-diagnosed, low-grade non-Hodgkin's lymphomas with unfavorable prognostic factors: results of a phase II study. Leuk Lymphoma 2004; 45: 93-100.
9 Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2006; 24: 1582-1589.
10 Tsimberidou AM, Mclaughlin P, Younes A, et al. Fludarabine, mitoxantrone, dexamethasone (FND) compared with an alternating triple therapy (ATT) regimen in patients with stage IV indolent lymphoma. Blood 2002; 100: 4351-4357.
11 Au WY, Ng WM, Choy C, et al. Aggressive subcutaneous panniculitis-like T-cell lymphoma: complete remission with fludarabine, mitoxantrone and dexamethasone. Br J Dermatol 2000; 143: 408-410.
12 Tse E, Chan JC, Pang A, et al. Fludarabine, mitoxantrone and dexamethasone as first-line treatment for T-cell large granular lymphocyte leukemia. Leukemia 2007; 21: 2225-2226.
13 Ma SY, Au WY, Chim CS et al. Fludarabine, mitoxantrone and dexamethasone in the treatment of indolent B- and T-cell lymphoid malignancies in Chinese patients. Br J Haematol 2004; 124: 754-761.
14 Wilder DD, Ogden JL, Jain VK. Efficacy of fludarabine/mitoxantrone/dexametha-sone alternating with CHOP in bulky follicular non-Hodgkin's lymphoma. Clin Lymphoma 2002; 2: 229-237.
15 Tsimberidou AM, Younes A, Romaguera J, et al. Immunosuppression and infectious complications in patients with stage IV indolent lymphoma treated with a fludarabine, mitoxantrone, and dexamethasone regimen. Cancer 2005; 104: 345-353.