Treatment of cutaneous T-cell lymphomas with purine analogues (fludarabine and 2-chlorodeoxyadenosine)

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Summary

Purpose: The aim of this study was to evaluate the efficacy and toxicity of the purine analogues 2-chlorodeoxyadenosine (2-CdA) and fludarabine (FAMP) combined with cyclophosphamide (CY) in the treatment of stage III and IV cutaneous T-cell lymphoma (CTCL).

Patients and methods: From January 1998 to December 2002, 10 heavily pretreated patients with CTCL, hospitalized at the Department of Dermatology in Wroclaw, were administered monotherapy with 2-CdA (6 patients) or FAMP plus CY combination chemotherapy (4 patients). 2-CdA was administered at a dose of 0.12 mg/kg daily for 7 days every 28 days. FAMP was administered at a dose of 25 mg/m² daily, days 1-3, and cyclophosphamide 400 mg/m², day 1. The combination was repeated every 28 days.

Results: Five out of 6 patients treated with 2-CdA showed a transient partial remission of the skin lesions lasting for a median of 2 months, and 1 patient showed disease progression with dissemination of the skin lesions. Of the 4 patients who received FAMP plus CY 1 achieved complete remission lasting for 6 months, and 2 attained a partial response lasting for a median of 3 months.

Conclusion: Purine analogues such as 2-CdA and FAMP may be used in the treatment of advanced stages of CTCL. The combination of FAMP plus CY, based on the restrictive effect of FAMP on the repair mechanisms of DNA damaged by CY, seems to be a promising therapeutic modality. Decreased immunity, leucopenia, thrombocytopenia and anaemia are common side effects of 2-CdA and FAMP.

Key words: 2-chlorodeoxyadenosine, cutaneous lymphoma, fludarabine, purine analogues

Introduction

Cutaneous lymphomas represent a heterogeneous group of T- and B-cell lymphomas that arise in the skin. Primary cutaneous lymphomas are defined with no evidence of extracutaneous disease for a period of at least 6 months after the diagnosis. Primary CTCL are more common than cutaneous B-cell lymphomas (CBCL), comprising 60-65% of all the cases [1]. The most frequent forms of CTCL are mycosis fungoides and Sézary syndrome. Four stages are distinguished, reflecting the disease evolution and spread. Staging is based on the evaluation of skin lesions, enlargement of lymph nodes, infiltration of internal organs and presence of Sézary cells in the blood [2]. The treatment of advanced stages of cutaneous lymphomas is systemic and is carried out either as monotherapy or combination therapy. It includes immunomodulators (interferon alpha) [3], retinoids (bexarotene, isotretinoin, acitretin) [4], and chemotherapeutic agents (methotrexate, cyclophosphamide). The most common combination therapies include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAVE (cyclophosphamide, doxorubicin, vincristine, etoposide), and EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) [5,6]. However, all of the standard thera-
pies used in the treatment of advanced stages of cutaneous lymphomas lead merely to transient remissions and so far are unable to provide complete and durable remissions. Thus new methods of therapy are being constantly searched for.

The mechanism of action of purine analogues consists in their incorporation into DNA and RNA. These agents cause cytotoxic effect and induce programmed cell death (apoptosis) [7]. In comparison to traditional antimetabolites, 2-CdA acts not only on actively dividing lymphocytes, but also on resting cells [8]. That is why 2-CdA produces good therapeutic results in the treatment of indolent lymphoproliferative diseases.

The purine analogues 2-CdA and FAMP are cytotoxic agents used in the treatment of chronic lymphoproliferative disorders. The greatest experience is from their use in the treatment of hairy cell leukemia, chronic lymphocytic leukemia and low-grade non-Hodgkin’s lymphomas [8-10]. Recently attempts have been undertaken to use 2-CdA and, in individual cases, FAMP, in the treatment of cutaneous lymphomas [11-15].

The aim of this study was to evaluate the efficacy and toxicity of 2-CdA and FAMP combined with CY in heavily pretreated patients with stage III and IV CTCL.

Patients and methods

From January 1998 to June 2002, 10 patients with progressive stage III and IV CTCL, hospitalized at the Department of Dermatology in Wroclaw, were administered either monotherapy with 2-CdA or FAMP plus CY combination chemotherapy. The following exclusion criteria were used in selecting patients: renal and liver insufficiency, heart failure, the presence of active infection, life expectancy less than 4 weeks, platelet count below 50000/ml, CD4 lymphocyte count below 0.3/ml. Prior to treatment initiation, routine full blood count, serum biochemistry, chest x-rays and abdominal ultrasound were performed. All patients had received prior chemotherapy before entering this study (Table 1 and 2).

2-CdA (Biodribin, Bioton) was administered at a dose of 0.12 mg/kg/day as a 2-hour infusion for 7 consecutive days. The cycles were repeated every 28 days, and the patients received from 2 to 5 cycles.

FAMP (Fludara, Schering AG) was administered at a dose of 25 mg/m²/day as a 30-min infusion, days 1-3 and cyclophosphamide 400 mg total dose i.v. bolus, day 1. The cycles were repeated every 4 weeks and the patients received from 2 to 8 cycles. In order to control infections, all of the patients received prophylactic oral cotrimoxazole 1× 480 mg/day for 14 days after the end of each chemotherapy cycle.

Results

Six patients with advanced stage of CTCL were treated with 2-CdA. The duration of disease on entering the study ranged from 3 to 10 years. All pa-

Table 1. Clinical and therapeutic data of patients treated with 2CdA

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age/sex</th>
<th>Disease duration (years)</th>
<th>Stage</th>
<th>Previous treatment</th>
<th>2-CdA (cycles)</th>
<th>Effect of 2-CdA therapy</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/M</td>
<td>8</td>
<td>IVA</td>
<td>PUVA, corticosteroids, methotrexate, azathioprine, ATRA, interferon, etoposide</td>
<td>3</td>
<td>transient partial improvement of skin lesions</td>
<td>herpes zoster, pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>82/F</td>
<td>3</td>
<td>IVA</td>
<td>corticosteroids, methotrexate, etoposide, epirubicin</td>
<td>2</td>
<td>transient partial improvement of skin lesions</td>
<td>leucopenia, thrombocytopenia, bacterial infections, sepsis</td>
</tr>
<tr>
<td>3</td>
<td>52/F</td>
<td>4</td>
<td>IVB</td>
<td>mitoxantrone, etoposide, ATRA, interferon alfa, hydrocortisone</td>
<td>2</td>
<td>disease progression</td>
<td>leucopenia</td>
</tr>
<tr>
<td>4</td>
<td>75/F</td>
<td>2</td>
<td>IVB</td>
<td>3 cycles CHOP, mitoxantrone, etoposide, corticosteroids</td>
<td>4</td>
<td>transient partial improvement of skin lesions</td>
<td>thrombocytopenia, sepsis</td>
</tr>
<tr>
<td>5</td>
<td>71/M</td>
<td>1</td>
<td>IVA</td>
<td>methotrexate</td>
<td>4</td>
<td>transient partial improvement of skin lesions</td>
<td>pneumonia between cycles, generalized herpes zoster</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>4</td>
<td>IIB</td>
<td>methotrexate, corticosteroids, PUVA</td>
<td>5</td>
<td>transient partial improvement of skin lesions</td>
<td>—</td>
</tr>
</tbody>
</table>

M: male; F: female; ATRA: all trans retinoid acid; PUVA: psoralen plus ultraviolet A; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone
tients had been treated previously with psoralen plus ultraviolet A (PUVA), methotrexate, corticosteroids or had received combination therapy according to established regimens (Table 1). Five patients achieved a transient remission of the skin lesions (Figure 1) of 2-month median duration (range 1-5 months). One patient showed dissemination of the specific skin lesions. Bacterial and viral infections were observed in 5 out of 6 patients treated with 2-CdA. Grade 3-4 leucopenia and thrombocytopenia was observed in 6 (30%) out of 30 cycles of 2-CdA. Only one patient tolerated treatment very well.

Four patients with advanced stage of CTCL received combination chemotherapy with FAMP plus CY. The disease had lasted from 2.5 to 10 years prior to treatment administration. All of the patients had been previously treated with PUVA, corticosteroids, methotrexate or combination chemotherapy (Table 2). Good

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age/sex</th>
<th>Disease duration (years)</th>
<th>Stage</th>
<th>Previous treatment</th>
<th>FAMP-CY (cycles)</th>
<th>Effect of FAMP-CY therapy</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/M</td>
<td>2.5</td>
<td>IVA</td>
<td>PUVA, CHOP-1 cycle</td>
<td>8</td>
<td>complete remission of erythrodermia after 3 cycles</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>39/M</td>
<td>4</td>
<td>IVB</td>
<td>PUVA, CVP 5 cycles, etoposide, amsacrine, mitoxantrone, corticosteroids, ATRA, interferon alfa</td>
<td>5</td>
<td>decreased erythema and itching</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>55/M</td>
<td>3</td>
<td>IVA</td>
<td>PUVA, corticosteroids, methotrexate, vinblastine, radiotherapy</td>
<td>2</td>
<td>partial remission of skin lesions</td>
<td>impetiginization after 2 cycles, sepsis</td>
</tr>
<tr>
<td>4</td>
<td>44/M</td>
<td>10</td>
<td>IVB</td>
<td>PUVA, corticosteroids, methotrexate, radiotherapy</td>
<td>4</td>
<td>partial remission of skin lesions</td>
<td>sepsis 3 weeks after the last cycle</td>
</tr>
</tbody>
</table>

M: male; F: female; ATRA: all trans retinoid acid; PUVA: psoralen plus ultraviolet A; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CVP: cyclophosphamide, vinblastine, prednisone

**Figure 1.** Patient before (A) and after (B) 2-CdA chemotherapy.
therapeutic result was obtained in 3 out of 4 patients and the treatment was well tolerated. One of these patients with a relatively short duration of the disease (2.5 years), treated previously with PUVA and 1 cycle of CHOP, received 8 courses of FAMP plus CY. After the 3rd course, his skin lesions and erythrodermia went into complete remission, with disappearance of the itching of the skin, which lasted for 6 months. The second patient had received PUVA, and many cycles of combination chemotherapy prior to FAMP plus CY treatment (Table 2). He received 5 cycles of FAMP plus CY, which resulted in a significant improvement of his condition (Figure 2). No significant haematologic toxicity was observed. The patient arbitrarily abandoned his therapy and died 5 months after the last cycle of chemotherapy of disseminated herpes zoster infection. The remaining 2 patients treated with FAMP plus CY achieved partial improvement of their skin lesions of 3-month median duration (range 1-6 months), but this was accompanied with decreased immunity and generalized infections. The results are presented in Table 2.

Discussion

No universal therapeutic scheme for cutaneous lymphomas has been established so far. The decision which therapy to choose depends on the clinical stage and the general condition of the patient. Previous treatment, especially cytotoxic agents, which may decrease the inherent compromised immunity should be taken into consideration.

As indicated by long-term clinical observations, early detection of primary cutaneous lymphoma as well as treatment of the initial stages of the disease (when infiltrations cover less than 10% of the body surface) give positive results and may be associated with a survival of more than 10 years [2]. However, advanced stages (T3-presence of tumours; T4-erythrodermia) have unfavourable prognosis. The average life expectancy in both stages is 3 years. The treatment consists of chemotherapy including several cytotoxic agents in combination with corticosteroids. Relapse is observed in the majority of the patients within few months. Moreover, a significantly compromised immune system during aggressive chemotherapy can lead to life-threatening infections. The patients often die because of pneumonia or sepsis.

Lack of effective therapy of advanced stages of cutaneous lymphomas has led to the search for new treatment modalities. Immunomodulating therapies, which are currently in experimental phase, include subcutaneous or intrafocal injections of IL-2, IL-12 [16], radioactive anti-CD4 monoclonal antibodies [17], vaccines against neoplastic cells and autologous bone marrow transplantation [2].

The attempts to use purine analogues in the treatment of CTCL were undertaken after the observation

Figure 2. Patient before (A) and after (B) FAMP plus CY chemotherapy.
of their beneficial therapeutic effect in other lymphoproliferative disorders. These agents were used in the majority of studies in the treatment of chronic lymphocytic leukemia, including the T-cell form [11,12,14]. In two small studies which included patients with advanced stages of Sézary syndrome, purine analogues showed major activity in terms of response, but did not affect the patients’ survival [8,18]. The therapeutic results were promising, however further testing in larger groups of patients is required. FAMP as monotherapy and in combination with CY has been applied recently in few patients with CTCL [13,15,18]. The mode of action of this new combination is based on the restricting effect of FAMP on the repair mechanisms of DNA, which had been damaged by CY. A similar therapeutic scheme of FAMP plus CY was applied with good results in the treatment of chronic lymphocytic leukemia [19]. In our study, 4 patients in advanced stage of CTCL were treated with FAMP plus CY combination chemotherapy. Two of them showed good therapeutic response - one partial regression of skin lesions and one complete remission. In these two cases chemotherapy was well tolerated.

In the study by Saven et al. the overall response rate in 15 patients with CTCL treated with 2-CdA was 47% [14]. In our study 5 out of 6 patients with advanced stage of CTCL treated with 2-CdA achieved a transient partial remission of the skin lesions. None of the patients achieved complete disease remission.

2-CdA and FAMP are generally well tolerated, as evidenced in the relevant literature. Decreased immunity, secondary infections and myelosuppression are the most important undesirable effects of chemotherapy with purine analogues [9]. We observed a relatively high rate of side effects, especially infections. Five out of 6 patients treated with 2-CdA developed viral or bacterial infections. Bone marrow suppression was observed in 3 patients. Two other patients treated with FAMP plus CY developed generalized infection and died. However, we must emphasized that all of our patients had been heavily pretreated.

Purine analogues such as 2-CdA and fludarabine may be used in the treatment of advanced stages of CTCL. The new combination of FAMP plus CY, based on the restrictive effect of FAMP on the repair mechanisms of DNA damaged by CY, seems to be a promising therapeutic approach. Decreased immunity, leucopenia, and thrombocytopenia are common side effects of 2-CdA and FAMP, which may sometimes be life threatening.

References