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Pentostatin in peripheral T-cell lymphomas

A B S T R A C T

Peripheral T-cell lymphomas (PTCL) comprise a heterogeneous group of diseases with different clinical presentation and morphologic, immunophenotypic and cytogenetic markers. Many of these malignancies follow an aggressive course and current therapeutic strategies are limited. The prognosis for these patients is usually very poor. The purine analogues are a class of drugs that have been shown to be active in patients who have T-cell lymphoma. T-cells have a very high concentration of adenosine deaminase, a key enzyme in the purine degradation pathway, which is blocked by this class of agent. Pentostatin has been the most extensively studied in PTCL and has shown variable response rates. However, many of the reports are limited to small single-center studies. Larger prospective randomized trials will be necessary to examine this therapy and to further explore combination regimens, which may result in increased responses.

Introduction

The purine analogues are one of the most active classes of drugs in patients with T-cell lymphoma. T-cells have high levels of adenosine deaminase (ADA), a key enzyme in the purine degradation pathway. The potential role of purine analogues was first identified based on the observation that children with congenital deficiency of ADA, had impaired lymphoid development.[1] This initiated the search for agents which might interfere with ADA activity. The purine analogues, including pentostatin, fludarabine, and cladribine, are a group of structurally similar agents that were developed to target ADA. Although they differ in their action, ultimately they all result in impairment of DNA repair. Thus they have synergy with cytotoxic agents (e.g. alkylating agents) that cause DNA damage. Pentostatin is a tight binding inhibitor of ADA. It blocks the deamination of adenosine to inosine and of deoxyadenosine to deoxyinosine leading to accumulation of deoxyadenosine and deoxyadenosine triiphosphate.[2] These metabolites block DNA synthesis through the inhibition of ribonucleotide reductase.

In the earliest clinical trials pentostatin was used in high doses to treat patients with T-ALL.[3] This was associated with treatment-limiting toxicities. Since that time pentostatin in lower, well tolerated, doses has shown remarkable activity in patients with hairy-cell leukemia, CLL, low-grade B-cell

malignancies as well as in PTCL.[4] The commonly used schedule now is intravenous administration of pentostatin at 4 mg/m^2 given every 1-2 weeks. Other higher dose schedules have also been used in reported studies. Dose adjustments are required if renal function is impaired.

Pentostatin therapy in T-cell malignancies

The majority of data evaluating pentostatin in T-cell lymphomas is based on trials in cutaneous T-cell lymphoma (CTCL). There are also reports that support the activity of these agents in other mature T-cell malignancies (Table 1). In the early 1980s, there were small reports describing the effectiveness of pentostatin in patients with T-cell leukaemias, including patients refractory to other therapy.[3-8] The European Organization for Research and Treatment for Cancer Leukemia Cooperative Study Group (EORTC) conducted a Phase II trial that included 76 patients with advanced T-cell malignancies, including 25 patients with what was then termed "T-CLL".[9] (Table 1) The response rate with pentostatin was 8% with a median disease free survival of 22 weeks. T-CLL has been re-classified by WHO as T-PLL, which has been shown in other studies to be responsive to pentostatin. The first case study was published in 1986, showing that two patients achieved remission following pentostatin.[10] In the early 1990's, Matutes *et al*.[11] published a report of 78 patients with T-PLL describing the clinical and laboratory features of the disease. Of the 78 patients, 31 were treated with pentostatin. There were 15 responses (48%) including 3 complete responses (CR) and 12 partial responses (PR). Patients with a T-helper-cell phenotype, $CD4^+CD8^-$, had a slightly better outcome

Table 1. Summary of pentostatin studies in peripheral T-cell lymphomas.

Study	*Pentostatin dose*	*Total # patients*	*Patient subset*	*CR(%)*	*PR(%)*	*OR(%)*	*Median overall survival*
Ho[9]	4 mg/m^2 Q wk x 3 then Q2wks x 6 then Q mo x 6	N=76 (T-cell NHL)	T-CLL = 25	0	8	8	DFS = 22 weeks
Matutes[11]	4 mg/m^2 Q wk	N=78 (T-PLL)	Pentostatin Treated = 31	9	39	48 (58)*	16 months (responders) 10 months (non-responders) 7 months (patients not Treated with Pentostatin)
Dohner[12]	4 mg/m^2 Q wk x 3 then Q 2wk x 3; If PR, Q mo x 6	N=20 (B & T-PLL)	T-PLL = 6	0	33	33	N/A
Dearden13	4 mg/m^2 Q wk x 4 then Q 2wk till Optimal response	N=68 (T-cell NHL)	T-PLL = 31 ATLL = 20 LGL = 4	9 10 25	39 5 0	48 (58)* 15 (18)* 25 (50)*	T-PLL (10-16 mos) ATLL (N/A) LGL (N/A)
Mercieca[15]	4 mg/m^2 Q wk x 4 then Q2wk till optimal response	N=145 (T-cell NHL)	T-PLL = 55 LGL = 5 ATLL = 25	9 40 8	40 0 4	45 40 12	N/A
Tsimberidou[16]	5 mg/m^2/da yx 3 days q 3 weeks	N=42	PTCL = 4 ATLL = 3 ALCL = 1	50 0 0	50 33 0	100 33 0	Median 4 months (1-61)

*OR, overall response rate; CR = complete response; PR, partial response; qwk, every week; mos, months; DFS, disease free survival; N/A, not reported; T-PLL, T-cell prolymphocytic leukemia; ATLL,adult T-cell leukemia lymphoma; LGL, T-cell large granular lymphocytic leukemia; PTCL, peripheral T-cell lymphoma; ALCL,anaplastic large cell lymphoma. *combination therapy.*

(response rate = 58%). Overall there were no prolonged remissions. Another Phase II study conducted by the EORTC treated 20 patients with T- or B-prolymphocytic leukemia with weekly pentostatin.[12] Of the 20 patients, six patients had T-PLL. There were 9 overall responders in the entire study population (45%) including 2 (33%) of the patients with T-PLL. All of the responses were partial (PR) and the median duration of response was 9 months (range 2-30 months). The majority of patients (85%) enrolled in this study had received prior chemotherapy.

By far the largest published experience with pentostatin in mature T-cell malignancies has been at the Royal Marsden Hospital in London.[13-15] (Table 1) A total of 165 patients who had a range of relapsed/refractory post-thymic T-cell malignancies received pentostatin at a dose of 4 mg/m^2 weekly for 4 weeks and then every two weeks until maximal response. Responses were seen in 34% of patients with a median response duration of 6 months (range 3 months to 15 years). Some patients had durable remissions, with disease subtypes the main predictor of response; T-PLL and Sézary syndrome had the best response rates of 45% and 62%, respectively. Only a minority (<10%) of these responses were complete. Although some of the remissions have been prolonged (up to 15 years in a SS patient) most patients relapsed within 1 year.[15] Activity in ATLL was disappointing and this has been confirmed by a number of studies in Japan.

Tsimberidou *et al.*[16] published the most recent report of pentostatin in PTCL, using a different dose schedule (5 mg/m^2 x 3 days). (Table 2) Forty-two patients including 32 (76%) with mycosis fungoides/Sézary syndrome and 10 patients (24%) with other T-cell leukemias or lymphomas were enrolled. The overall response rate was 54.8% (CR=14.3% and PR=40.5%). Durable responses were observed mainly in patients with Sézary syndrome or peripheral T-cell lymphoma. The

Table 2. Summary of trials of pentostatin in CTCL.

Study	*Pentostatin dose*	*N*	*CR(%)*	*PR(%)*	*OR(%)*	*Duration of response*
Ho9	4 mg/m^2 Q wk x 3 then Q2wks x 6 then Q mo x 6	21SS 22MF	5 0	28 23	33 23	
Dearden[13]	4 mg/m^2/wk x 4 then QOW	7SS 6MF	14 0	86 0	100 0	(not reported)
Mercieca[15]	4 mg/m^2 Q wk x 4 then Q2wk till optimal response	16SS 4SL 13MF	19 0 0	44 50 0	63 50 0	9 mo for SS
Grever[17]	4 mg/m^2 x 3 days then monthly	18	11	22	33	CR (7-10mos); PR (1-3mos)
Cummings[18]	5 mg/m^2 x 3 days, q 3 wks	6	0	67	67	
Greiner[19]	4 mg/m^2 QOW	18	11	28	39	CR (4mos-6yrs); PR (1.5-6mos)
Kurzrock[20]	3.75-5 mg/m^2/dayx 3 days q 3 weeks	24	29	43	71	3.5 mos for SS 2 mos for MF
*Foss[31]	Alternating w/ IFN	41	5	37	42	15.8mos

OR, overall response rate; CR, complete response; PR, partial response; qwk, every week; mos, months; DFS, disease free survival; N/A, not reported.
**combination therapy.*

median duration of response was 4.3 months (range 1-61 months).

Several other smaller studies of pentostatin as a single agent in previously treated CTCL showed an overall response rate of approximately 50% (range 26-100%)[17-20] (Table 2). The first report was by Grever *et al*.[17] in 4 patients with advanced refractory MF, with 2 achieving CR and 2 PR. Subsequent trials did not confirm these high response rates for MF with responses (mostly PR) seen in 0-57%. The distinction was not always clear between MF and SS in these studies but, where stated, the best responses were seen in erythrodermic CTCL/SS. Again, response rates appear to be dose-related.

There have been numerous case reports of successful treatment of other, rarer, T cell malignancies, including T-large granular lymphocyte (LGL) leukaemia,[21-23] hepatosplenic T-cell lymphoma[24-26] and granulomatous slack skin disease.[27] There has also been a suggestion that CD26 expression on the malignant T cells predicts for poor response to pentostatin.[28,29] Further, the presence of activation markers such as CD25, CD38 and CD103, predict for increased sensitivity to purine analogues.[30]

Combination therapy

A study combining pentostatin with interferon-α for treatment of refractory CTCL showed an increased response rate compared with historic data using pentostatin alone, with a response duration of 13 months.[31]

Monoclonal antibody therapy is also emerging as a promising approach to treating PTCL. The anti-CD52 antibody alemtuzumab is an effective therapy in PTCL and has produced durable responses in two-thirds of heavily pretreated patients with T-PLL.[32] There is some limited experience of the combination of pentostatin and alemtuzumab[33] and this deserves further exploration. However, the increased risk of infection must be considered.

There are other agents which have also shown single agent activity in small numbers of patients with PTCL, including anti-CD4 and anti CD25 monoclonal antibodies, denileukin diftitox (ONTAK), bexarotene and histone deacetylase (HDAC) Inhibitors. Further study will be necessary to delineate the role of any of these agents in combination with purine analogues.

Conclusions

PTCL are a diverse group of diseases with varying clinical manifestations and courses. Response to traditional chemotherapy is poor. The data evaluating pentostatin in patients with PTCL is limited to small, non-randomized single center studies. The response rates in patients with relapsed/refractory disease have varied with monotherapy between 25% and 60%. The majority of data in T-cell disease is in CTCL with very limited data available for the other disease subtypes. Combination therapy with purine analogues and other agents, particularly monoclonal antibodies or small molecule inhibitors, will need to be explored in the future in order to see increased response rates, although this must be balanced with the potential increased toxicities. The role of pentostatin, alone or in combination, in previously untreated patients with PTCL has yet to be established.

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