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REVIEW

Critical appraisal of pralatrexate in the management of difficult-to-treat peripheral T cell lymphoma

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Abstract: Aggressive T cell lymphomas are a subgroup of lymphomas with a particularly poor prognosis. This is especially true for patients with recurrent or refractory disease, who typically have limited response to salvage therapy and extremely poor overall survival. For this reason, there is a strong need to develop potentially active drugs for these malignancies. Pralatrexate is a novel antifolate designed to have high affinity for reduced folate carrier type 1. Preclinical and clinical studies have demonstrated that pralatrexate has significant activity against T cell lymphomas. The dose-limiting toxicity for pralatrexate is mucositis, which can be abrogated with folic acid and vitamin B12 supplementation. Pralatrexate is the first single agent approved for the treatment of patients with relapsed or refractory peripheral T cell lymphoma. This approval was based on an overall objective response rate observed in the pivotal study. The overall response rate was 29%, with a median duration of 10.1 months. This article reviews the biochemistry, preclinical experience, metabolism, and pharmacokinetics of pralatrexate, including the clinical experience with this agent in lymphoma. Future areas of development are now focused on identifying synergistic combinations of pralatrexate with other agents and the evaluation of predictive markers for clinical benefit.

Keywords: pralatrexate, peripheral T cell lymphoma

Introduction

Over the past 30 years, there has been an increasing understanding of the genetic abnormalities and immunological characteristics of non-Hodgkin's lymphoma (NHL). This knowledge has led to further subclassification of NHL, with the recognition of new subtypes within both the B cell and T cell categories. In 1994, a group of European and US pathologists proposed a new classification of lymphoid neoplasms based upon contemporary morphological, immunological, and genetic techniques.[1] This eventually formed the basis for a new World Health Organization classification of the hematopoietic and lymphoid neoplasms, utilizing many of the new diagnostic techniques in an attempt to recognize all of the existing and new entities.[2] This new classification system was tested in a cohort of 1403 cases of NHL obtained worldwide in the International Non-Hodgkin Lymphoma Classification Project.[3] Of these cases, only 7% represented a subtype of peripheral T cell lymphoma (PTCL), and 2.4% were anaplastic large T/null cell lymphoma. However, even in a study of this size, too few cases were present to investigate the various subtypes of PTCL. In Western countries, PTCL accounts for 15%–20% of aggressive lymphomas and 5%–10% of all NHLs.[4] In Asia, this number is higher, with 15%–20% of all lymphomas classified as PTCL or natural killer T cell lymphoma (NKTCL).[4] A large international retrospective

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study[5] evaluated the various subtypes of lymphoma and other disorders found among cases from 22 sites in the US, Europe, and Asia. The subtypes documented upon review are found in Table 1.

The majority of patients with PTCL present with advanced disease, and one third have extranodal involvement at the time of diagnosis. The overall survival for many of the subtypes of PTCL and NKTCL is poor. Most aggressive PTCLs and NKTCLs have traditionally been treated with an anthracycline-containing regimen, and complete response rates of 50%–70% have been reported.[6,7] However, patients in these studies have a long-term survival of only 10%–30%. The recent international study confirms the very poor prognosis of patients with aggressive forms of PTCL and NKTCL. For the most common subtypes, PTCL not otherwise specified (NOS) and angioimmunoblastic lymphoma, patients treated with an anthracycline-containing regimen had the same long-term survival as those treated with nonanthracycline-containing regimens.[5] Unfortunately, the failure-free survival of patients with high-risk or intermediate-high risk disease ranges from 0% to less than 10%, with virtually no long-term survivors.[8–10] In one such study,[10] the complete response rate for patients with NKTCL was only 43%, while nearly half of all patients were refractory to their initial upfront chemotherapy.

Collectively, these observations strongly suggest that patients with T cell lymphoma are in urgent need of additional new treatment options. This is especially true for patients with recurrent or refractory disease who typically have limited response to salvage therapy and extremely poor overall survival. Pralatrexate is one agent that, based on strong preclinical and clinical data, is emerging as a promising new drug for the treatment of drug-resistant T cell lymphoma.[11] In a Phase II lymphoma study, pralatrexate demonstrated activity against PTCL. Subsequently, a multicenter Phase II study has led to the approval of pralatrexate in the US for relapsed or refractory peripheral T lymphomas.[13] The purpose of this review was to perform a critical analysis of this drug, considering its advantages and disadvantages.

Table 1 Distribution of 1314 cases of aggressive T cell lymphoma by consensus diagnosis[5]

Peripheral T cell lymphoma, NOS	25.9%
Angioimmunoblastic T cell lymphoma	18.5%
Natural killer/T cell lymphoma	10.4%
Adult T cell leukemia/lymphoma	9.6%
Anaplastic large cell lymphoma, ALK+	6.6%
Anaplastic large cell lymphoma, ALK–	5.5%
Enteropathy-type T cell lymphoma	4.7%
Primary cutaneous anaplastic large cell lymphoma	1.7%
Hepatosplenic T cell lymphoma	1.4%
Subcutaneous panniculitis-like T cell lymphoma	0.9%
Unclassifiable peripheral T cell lymphoma	2.5%
Other disorders	12.2%

Abbreviations: NOS, not otherwise specified; ALK, anaplastic lymphoma kinase.

Biochemistry, pharmacology, and preclinical experience

Inhibition of the folate enzymes, dihydrofolate reductase and thymidylate synthase, is a well validated method of cancer treatment. Several antifolate anticancer agents, including methotrexate, pemetrexed, and raltitrexed, act via inhibition of these enzymes.[12] Dihydrofolate reductase reduces dihydrofolic acid to tetrahydrofolic acid, a compound that is required by dividing cells for the synthesis of thymine. Reduced thymine levels following dihydrofolate reductase inhibition prevent cell division in rapidly dividing cancer cells.[12] The cellular uptake of antifolate agents is mediated by reduced folate carrier 1 (RFC-1), and the antifolates are retained intracellularly via polyglutamylation then catalyzed by folylpoly-gamma-glutamate synthetase.[14] Methotrexate, which uses this pathway, has been used to treat various types of NHLs, eg, diffuse large B cell lymphoma, Burkitt's lymphoma, and primary central nervous system lymphomas.[15,16]

Tumor cell mutations that inhibit the polyglutamylation cellular retention mechanism are a common method of tumor resistance to methotrexate.[14,17] Thus, compounds with a greater affinity for RFC-1 (to improve membrane transport) and folylpoly-gamma-glutamate synthetase (to enhance polyglutamylation and, therefore, intracellular retention) than methotrexate have been designed to enhance antitumor activity.[18]

Pralatrexate is a 10-deazaaminopterin derivative that was determined to be a more potent inhibitor of dihydrofolate reductase than methotrexate. The improved activity is due to the more effective internalization by RFC-1 and subsequent accumulation in tumor cells through the formation of polyglutamylated metabolites. These biochemical features suggest that pralatrexate should be a more potent antineoplastic agent in comparison with methotrexate and could overcome known mechanisms of methotrexate resistance, such as downregulation of RFC-1 and/or folylpoly-gamma-glutamate synthetase. The cytotoxicity of pralatrexate and methotrexate was compared in parallel in four NHL cell lines by the Memorial Sloan Kettering Cancer Center group.[19] These studies (summarized in Table 2) included the following cell lines: RL, a transformed follicular lymphoma overexpressing bcl-2; HT,

Table 2 Cytotoxicity of pralatrexate and methotrexate across a panel of aggressive non-Hodgkin's lymphoma cell lines[21]

Cell line	Lymphoma subtype	Pralatrexate IC_{50} value (nmol/L)	Methotrexate IC_{50} value (nmol/L)	*P* value
HS445	Hodgkin's disease	1.6 ± 0.08	32 ± 2.2	0.0455
HT	DLBCL	3.0 ± 0.4	35 ± 5	0.0236
RL	Transformed large cell lymphoma [t(14:18)]	23 ± 2	210 ± 40	0.0429
SKI-DLBCL	DLBCL (ascites)	5.1 ± 0.1	48 ± 2.5	0.0035
Raji	Burkitt's lymphoma	2 ± 0.3	16 ± 0.8	0.0034

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

a diffuse large-cell lymphoma; Hs602, a B cell lymphoma derived from a mixed-cell NHL; and SKI-DLCL-1, a diffuse large-cell lymphoma overexpressing MUC-1. In all cases, pralatrexate exhibited 10-fold greater cytotoxicity than methotrexate.[19]

The in vitro experiments demonstrated that pralatrexate consistently produced IC_{50} values 1 log below that typically seen for methotrexate in a library of lymphoma cell lines representing a number of different diseases, including diffuse large B cell lymphoma, T cell lymphoma, mantle cell lymphoma, and even a very chemotherapy-refractory transformed lymphoma carrying the 14:18 translocation.

Another study[20] investigated the potential mechanistic differences between pralatrexate and other antifolates, specifically methotrexate and pemetrexed, in NCI-H460 nonsmall cell lung cancer cells and MV522 and NCI-H460 human nonsmall cell lung cancer xenografts. A significantly greater proportion of radiolabeled pralatrexate entered the cells and was polyglutamylated relative to methotrexate and pemetrexed. In vivo, pralatrexate showed superior antitumor activity in both nonsmall cell lung cancer models, with more effective dose-dependent tumor growth inhibition in the more rapidly growing NCI-H460 xenografts.

Pralatrexate was also consistently found to be superior to methotrexate in vivo. In a NOD-SCID xenograft model of these lymphomas, complete regression of disease was observed in mice bearing HT lymphoma following treatment with pralatrexate, while methotrexate-treated mice experienced only a 17% reduction in tumor growth. In the RL lymphoma xenograft model, mice treated with pralatrexate exhibited significant tumor regression, with two thirds of the mice in the pralatrexate-treated group experiencing a complete regression of disease, while mice treated with methotrexate experienced only a modest growth delay compared with the control group.[21]

Interestingly, characterization of these cell lines by quantitative reverse transcription polymerase chain reaction for a number of the determinants of antifolate activity (RFC-1, folylpoly-gamma-glutamate synthetase, gamma-glutamyl hydrolase) revealed a striking correlation between the level of RFC-1 expression and the incidence of complete remission in the NOD-SCID mouse models, with no instances of complete remission observed in any methotrexate-treated mouse cohort (Table 3).[21]

Based upon the single-agent activity of pralatrexate in previously reported studies, a series of experiments exploring the integration of pralatrexate with new-generation cytidine analogs, most notably gemcitabine, revealed that these two agents appear to be synergistic in mouse models of lymphomas.

One of the important observations from these studies[22] revolved around the importance of the marked schedule dependency. As has been demonstrated for methotrexate and cytarabine,[22,23] there appears to be a consistent demonstration of schedule dependency with pralatrexate and gemcitabine as well.

A study of pralatrexate administration in combination with gemcitabine in a panel of lymphoma cell lines demonstrated that this combination is not only synergistic and more efficient than methotrexate/gemcitabine in generating apoptosis, but also that the effects were highly sequence-dependent.[24] These data provide a very strong rationale for combining pralatrexate with gemcitabine in future clinical trials.

Metabolism and pharmacokinetics

Following weekly and biweekly administrations of intravenous pralatrexate (escalating doses beginning from 30 mg/m^2) to 33 patients with advanced nonsmall cell lung

Table 3 Correlation between complete remission rates to pralatrexate and reduced folate carrier type 1 expression in a xenograft model of non-Hodgkin's lymphoma with different cell lines[21]

Cell line	Level of expression of RFC-1	Complete response to pralatrexate
HT	0.96[a]	90%[a]
RL	0.41[a]	55%[a]
SKI-DLBCL	0.3[a]	30[a]

Notes: [a]All differences were statistically significant; data from O'Connor.[21]

cancer in a Phase I clinical trial, the mean area under the curve (AUC) values after initial doses of 30, 120, 130, 150, and 170 mg/m^2 were 5.0, 8.2, 29.8, 20.6, and 30.6 μmol · h, respectively. The mean terminal half-life at a dose of 150 mg/m^2 was eight hours. No changes were observed from the first dose to the second dose on the weekly or biweekly schedule. Chromatography analysis demonstrated the presence of a metabolite, which had a low peak level that did not change between days 1 and 15, indicating that no induction or inhibition of metabolism had occurred. Urinary excretion, measured in two patients, was 6% and 20% at 24 hours.[26]

Pharmacokinetic data from 47 patients with hematological malignancies receiving intravenous pralatrexate weekly (30–45 mg/m^2) or biweekly (135–240 mg/m^2) in a Phase I/II clinical trial were modeled in a three-compartment linear model. Patient weight and methylmalonic acid (an indicator of vitamin B deficiency) were determined to be predictive of interpatient pharmacokinetic variability. Increased AUC levels for pralatrexate and methylmalonic acid were also predictive of toxicity. The pharmacokinetic model assisted in identifying the safest dosing schedule for pralatrexate and supported the need for vitamin supplementation.[27] An open-label, nonrandomized Phase I clinical trial assessed whether supplementation of vitamin B12 and folic acid increased the maximum tolerated dose of pralatrexate.[11] A total of 22 patients with nonsmall cell lung cancer received intramuscular vitamin B12 1 mg and oral folic acid 1 mg 7 days prior to receiving intravenous pralatrexate 150, 190, 230, 270, and 325 mg/m^2 every 2 weeks. The addition of vitamin B12 and folic acid was determined to allow higher doses of pralatrexate to be administered, and the maximum tolerated dose was increased to 270 mg/m^2.

Toxicity

The first Phase I study of pralatrexate[26] was conducted exclusively in patients with relapsed or refractory nonsmall cell lung cancer. Stomatitis became the dose-limiting toxicity, but when pralatrexate was supplemented with vitamin B12 and folic acid, stomatitis was reduced in severity and frequency.[11] Other common adverse events observed were mild, including a grade 2 elevation of alanine transferase and aspartate transferase (n = 3), a diffuse maculopapular, pruritic skin rash (n = 1), and reticulonodular pulmonary infiltrates (n = 1). Significantly, no neutropenia was observed.[26]

When pralatrexate treatment was supplemented with vitamin B12 and folic acid in patients with nonsmall cell lung cancer, no dose-limiting toxicities were observed at pralatrexate doses of 150–230 mg/m^2.[11] Grade 3 mucositis was reported in five of 16 patients receiving the 270 mg/m^2 dose and in two of three patients receiving the 325 mg/m^2 dose. Other common adverse events at all dose levels (n = 22) included grade 2 fatigue (n = 10), grade 1 nausea (n = 9), grade 1 vomiting (n = 4), and grade 1 rash (n = 4).[11]

In patients with hematological malignancies, 135 mg/m^2 of pralatrexate administered every 2 weeks was associated with an increased risk of high-grade mucositis and significant hematological toxicities, such as thrombocytopenia and leukopenia.[11] When the dosing schedule was modified to weekly doses of 30 mg/m^2 of pralatrexate, hematological toxicities were reduced by 50%, and no high-grade mucositis was observed. Vitamin supplementation also reduced the risk of mucositis.[11,28]

The majority of patients in the Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PROPEL) study tolerated pralatrexate. They received pralatrexate intravenously at 30 mg/m^2/week for 6 weeks in 7-week cycles. The overall relative dose intensity (delivered versus planned doses administered) was 80%. Seventy-six patients (68%) remained at the target dose of 30 mg/m^2 for the duration of treatment, and 76 (68%) had one or more dose omissions due to adverse events. Mucositis was the most common reason for dose modification. Specifically, 23% of patients required dose reduction for mucositis. Other reasons for dose reduction were abnormal liver function tests, thrombocytopenia, and fatigue (two patients each, 2%), and herpes zoster, leukopenia, neutropenia, and pruritic rash (one patient each, <1%). Forty-five percent (n = 50) experienced serious adverse events while in the study or ≤30 days after their last dose of pralatrexate. The most common serious adverse events included pyrexia (7%), mucositis (5%), febrile neutropenia (5%), sepsis (5%), dehydration (4%), and dyspnea (4%). The majority of adverse events were reversible or manageable by dose modification. No cumulative myelosuppression was observed with continued pralatrexate treatment. Thrombocytopenia, anemia, and neutropenia were rarely symptomatic and required supportive care in a minority of patients; 15% of patients received a platelet transfusion, and 10% received filgrastim.

Twenty-three percent (n = 26) withdrew from treatment due to adverse events, and eight (7%) died within 30 days

of their last dose of pralatrexate. Seven patients died due to progression of disease and one patient experienced a cardiopulmonary arrest approximately 3 weeks after the last dose of pralatrexate. This death was deemed possibly related to pralatrexate.[13]

Clinical experience with pralatrexate in lymphoma

A Phase I/II study of pralatrexate in patients with relapsed and refractory NHL and Hodgkin's lymphoma began in May 2002 at Memorial Sloan Kettering Cancer Center. Based on a Phase I study in patients with nonsmall cell lung cancer, the initial Phase II study of pralatrexate in lymphoma used a dose of 135 mg/m^2 administered as an intravenous bolus over 3–5 minutes every other week. A total of 16 patients were enrolled on this study, including 15 patients with B cell lymphoma and one with a PTCL NOS. This last patient enrolled in the study was a middle-aged male with a history of very chemotherapy-refractory PTCL NOS, who experienced a CT-negative and positron emission tomography-negative complete remission following one dose of pralatrexate.[21] This patient experienced the only durable response to pralatrexate known at that time. At this dose, pralatrexate was associated with significant grade 3 and 4 stomatitis, which was markedly greater than that appreciated in the previous nonsmall cell lung cancer studies.[26] Based on the observed toxicity, the study was amended to a Phase I/II study in which pralatrexate was scheduled weekly. Dose-limiting toxicity was seen at 45 mg/m^2, and thus, 30 mg/m^2 weekly × 6 weeks for every 7-week cycle was chosen as the maximum tolerated dose.[28]

On this revised schedule, 40 patients with Hodgkin's lymphoma, diffuse large B cell lymphoma, and T cell lymphoma were recruited (total n = 56 overall). In the most recent report of results for this trial, the overall response in 46 evaluable patients was 35%.[11] In patients with B cell and T cell lymphoma (n = 20 and n = 26 evaluable patients, respectively), the overall response rates were 10% and 54%, respectively. Complete remissions were observed in nine patients with T cell lymphoma, and partial remissions occurred in five patients and two patients with T cell and B cell lymphomas, respectively; the duration of remission was 3–24 months. Durable complete remissions were observed in the following subtypes of cancer: acute lymphoblastic (12 months), human T cell leukemia virus type 1 adult T cell leukemia/lymphoma (≥21 months; n = 3), blastic NKTCL (8 months), anaplastic lymphoma kinase (+) anaplastic large cell cancer (≥10 months), PTCL NOS (3 months), subcutaneous panniculitis-like T cell lymphoma (9 months) and γ, δ-subcutaneous panniculitis-like T cell lymphoma (9 months). Most of the responding patients had been refractory to previous chemotherapy, including methotrexate.

A case of a woman with a rare, highly aggressive CD4+ CD56+ hematodermic/plasmacytoid dendritic cell tumor has been reported. The tumor had relapsed quickly after previous treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and was treated with weekly intravenous doses of pralatrexate 30 mg/m^2 supplemented with folic acid and vitamin B12 every 4 weeks. After six infusions, a durable response was observed, and skin tumors regressed, indicating the potential use of pralatrexate for this malignancy.[30]

On September 24, 2009, the Office of Oncology Drug Products granted accelerated approval of pralatrexate injection for the treatment of patients with relapsed and refractory PTCL. This approval was based on the overall objective response rate observed in PROPEL. The PROPEL study was an open-label, nonrandomized, multicenter, international clinical trial that enrolled 115 patients with PTCL who had relapsed or had progressive disease following prior therapy. Sixty-three percent did not have an objective response to the most recent prior therapy. One hundred and nine evaluable patients received pralatrexate at a starting dose of 30 mg/m^2 administered as an intravenous push over 3–5 minutes once weekly for 6 weeks followed by a 1-week break (one cycle). In addition, each patient received vitamin B12 1.0 mg intramuscularly every 8–10 weeks and daily administration of folic acid 1.0–1.25 mg orally. Imaging scans to assess disease status were performed at week 7 (end of cycle 1) and subsequently at 14-week intervals. The primary endpoint of the study was overall response rate. In the evaluable patient population (n = 109), the overall response rate (complete remission plus complete remission unconfirmed plus partial response) was 29% (95% confidence interval [CI], 21–39), as assessed by independent central review. Twelve patients (11%) achieved a complete remission/unconfirmed complete remission, 20 (18%) achieved a partial response, and 21 (19%) experienced stable disease. Of the 26 patients who did not have responses to any prior conventional therapy, five (19%) responded to pralatrexate. The majority of responding patients responded quickly; 63% of all responses occurred within the first cycle of pralatrexate, but responses were observed as late as cycle 7. The median duration of response was 10.1 months, with a range of

1–673 days. Among the 32 responders, 16 (50%) progressed or died, five (16%) were still responding, and 11 (34%) were censored as follows: four transplants (two autologous and two allogeneic), subsequent therapy (n = 3), or study termination (n = 4). Interestingly, only two patients who attained a complete remission developed progressive disease. Nine patients had responses exceeding 300 days in duration, four of whom remained on treatment at the time of data cutoff. At the time of last follow-up, all four of the patients still in response (three complete remissions, one partial response) at the time of stem cell transplant (SCT) remained alive and had received no further therapy. The median progression-free survival was 3.5 months (95% CI 1.7–4.8), with a range of 1 day to 23.9 months. The median overall survival was 14.5 months (95% CI 10.6–22.5), with a range of 1.0 to 24.1 months. Forty-three percent were censored for overall survival because they were alive at the data cutoff date. The median follow-up time for all patients still alive at the time of the analysis was 18 months.[13]

Other analysis evaluated SCT use before or after pralatrexate in the PROPEL study. Of the 109 patients who were evaluable for response, six (6%) went on to SCT (two autologous SCT, four allogeneic SCT) as their initial subsequent therapy after responding to pralatrexate, according to investigator assessment of response. Four of these patients were still in response by central review at the time they started SCT. At the time of data cutoff, no additional therapy had been administered to any of these four patients following SCT. The other two patients had partial responses by investigator review and progressive disease by central review at the time SCT was started, and neither of these patients had additional therapy documented after SCT. All six patients were alive at the time of last contact.[32]

A US Food and Drug Administration review of the PROPEL data[31] indicated that only 13 (12%, 95% CI 7–20) of the responses were maintained for ≥14 weeks (time interval between scans). Sixteen of 29 responders had durations of response less than 14 weeks (10 developed progressive disease on subsequent scans, three had no subsequent imaging scans because of off-study treatment, and three responders were censored).

Combinations with other drugs

Pralatrexate and gemcitabine each have activity as monotherapy in patients with relapsed or refractory lymphoma. Preclinical data reported synergy for the combination of these drugs in NHL cell lines and xenografts that was schedule-dependent.[24] A multicenter Phase I/IIa study (PDX-009, NCT00481871) was initiated to evaluate this treatment combination. The primary objective of the Phase I portion was to determinate the maximum tolerated dose and optimal Phase II dose and schedule for the combination of pralatrexate and gemcitabine in patients with relapsed or refractory lymphoma.

As of May 2009, 34 patients were treated in the Phase I portion, including 24 men (71%), and the median age was 63 (range 19–81) years. Histology included 13 patients with B cell lymphoma, 11 with NKTCL, seven with Hodgkin's lymphoma, and three with "other" lymphoma. Patients had received a median of 3.5 (range 1–11) prior regimens. All patients with once-weekly sequential day dosing (pralatrexate 10–15 mg/m^2 and gemcitabine 300–400 mg/m^2) in group A had dose-limiting toxicities of thrombocytopenia and/or neutropenia. Therefore, accrual to this schedule was halted, and subsequent cohorts received pralatrexate with gemcitabine on a twice-weekly schedule (groups B and C). The maximum tolerated dose with the twice-weekly dosing schedule was pralatrexate/gemcitabine 10/400 mg/m^2 when given on sequential days (group B) and 15/600 mg/m^2 when given on the same day (group C). Of 33 patients who were evaluable for response, seven (21%) showed a partial response, including patients with Hodgkin's lymphoma (n = 4), diffuse large B cell lymphoma (n = 1), angioimmunoblastic T cell lymphoma (n = 1), and composite diffuse large B cell lymphoma and T cell lymphoma (n = 1). Responses were seen in patients treated on the same day as well as on the sequential day schedule. The dose-limiting toxicities for group B were cellulitis, pulmonary embolus, thrombocytopenia, and febrile neutropenia, and the dose-limiting toxicities for group C were fatigue, hypoxia, mucositis, and thrombocytopenia. Across all groups, the most frequently reported grade 3–4 pralatrexate-related adverse events were neutropenia (41%), thrombocytopenia (35%), anemia (29%), and leukopenia (12%). Treatment with pralatrexate and gemcitabine is feasible, with acceptable toxicity, when administered on a twice-weekly schedule. However, the maximum tolerated dose of each group is 50% greater when given on the same day compared with treating on sequential days. Phase 2 expansions of the maximum tolerated dose will explore both sequential-day dosing (10/400 mg/m^2) and same-day dosing (15/600 mg/m^2) in a twice-weekly schedule.[24]

Conclusion

The prognosis for patients with newly diagnosed aggressive PTCL is poor for most subtypes. PTCLs have the lowest 5-year survival rates among the NHL subtypes, including

mantle cell lymphoma. Clearly, better therapeutic regimens are needed to improve the long-term outcome of these patients. Pralatrexate, a novel aminopterin with high affinity for the reduced folate carrier, appears to demonstrate significant activity in a select subpopulation of patients with T cell lymphoma, including patients with a variety of precursors and PTCL. At this time, the clinical benefit of pralatrexate, such as improvement in overall or progression-free survival, has not been shown. However, the magnitude of the pralatrexate effect (ie, 12% responses lasting at least 14 weeks) most likely predicts clinical benefit in this previously heavily treated patient population (median of three prior therapies) with a rare disease, in which no therapies are currently approved.

Future areas of development have now focused on identifying synergistic combinations of other agents with pralatrexate, including gemcitabine, bortezomib, and histone deacetylase inhibitors. The problem has now evolved into an abundance of drugs with too few patients available for testing. Collaborative groups will aid in future efforts to find the best treatment strategies to improve the outcome for patients with PTCL.

Disclosure

The authors report no conflicts of interest in this work.

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