Clinical Medicine Insights: Oncology

REVIEW

Safety and Efficacy of Pralatrexate in the Management of Relapsed or Refractory Peripheral T-cell Lymphoma

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Abstract: Peripheral T-cell lymphoma (PTCL) represents a relatively rare group of heterogeneous non-Hodgkin lymphomas, with generally poor prognosis. Historically, there has been a lack of consensus regarding appropriate therapeutic measures for the disease, with conventional frontline chemotherapies being utilized in most cases. Following promising results obtained in 2009, the methotrexate analogue, pralatrexate, became the first drug to gain US FDA approval for the treatment of refractory PTCL. This antimetabolite was designed to have a higher affinity for reduced folate carrier (RFC) and folylpolyglutamate synthetase (FPGS). RFC is the principal transporter for cell entrance of folates and antifolates. Once inside the cell, pralatrexate is efficiently polyglutamated by FPGS. Pralatrexate has demonstrated varying degrees of efficacy in peripheral T-cell lymphoma, with response rates differing between the multiple subtypes of the disease. While phase III studies are still to be completed, early clinical trials indicate that pralatrexate is promising new therapeutic for PTCL.

Keywords: peripheral T-cell lymphoma, antifolate therapy, methotrexate, pralatrexate, folate metabolism

Clinical Medicine Insights: Oncology 2012:6 305–314

doi: 10.4137/CMO.S8536

This article is available from http://www.la-press.com.

Introduction

Peripheral T-cell lymphoma (PTCL) encompasses a spectrum of rare and aggressive non-Hodgkin lymphomas, contributing to approximately 10%–15% of all newly diagnosed non-Hodgkin's lymphoma cases.[1–3] The disease represents a heterogeneous group of clinicopathologically defined T-cell/natural killer (NK) lymphomas that develop from clonal proliferation of mature, post-thymic T-cells. According to the World Health Organization (WHO) there are currently 20 histological subtypes of PTCL, the most common being PTCL not otherwise specified (PTCL-NOS), followed by angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma (ATLL) and anaplastic large-cell lymphoma (ALCL).[2,3] The annual incidence of PTCL in the United States is estimated to be approximately 9500, with a higher prevalence among men (male-to-female ratio of 1.8:1), demonstrating significant geographic and racial differences in incidence.[4] The disease occurs more frequently in older individuals; the median age of diagnosis is 61 years.[5–8] Although it is a rare disease, those with PTCL demonstrate poor responses to conventional chemotherapy treatments, unlike patients with B-cell non-Hodgkin lymphomas. Hence, the outlook for these individuals is poor. A recent report from the International T-Cell Lymphoma Project outlined that survival rates for patients with PTCL was highly dependent upon the subtype of the disease. Of the patients included in this study, more than 85% had already undergone pre-treatment with an anthracycline-containing regimen, yet the overall five-year survival rate for patients was still poor, with the exception of ALK-positive ALCL. While the response rate for ALK-positive ALCL was 70%, the response rate for ALK-negative ALCL was 49%, for PTCL-NOS it was 32%, for AITL it was 32% and for ATLL it was 14%.[2,9,10]

Management of PTCL has been largely extrapolated from treatment regimes that are in place for aggressive B-cell lymphomas. Therapeutic responses to this approach have been shown to be neither adequate nor durable, having poor outcomes in the majority of patients. Ultimately, refractory disease following a variety of agents, including multi-agent chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like regimens, has ensued.[11] In an attempt to explore the efficacy of these treatments, a recent report by the International T-cell Lymphoma Clinical/Pathologic Project provided evidence that unlike for B-cell lymphoma, there was no difference in overall survival (OS) rates between patients with PTCL who underwent CHOP therapy and those that did not.[2] It is not understood why patients with aggressive T-cell lymphomas show lower response rates to conventional B-cell lymphoma regimens. One possibility is that increased expression of drug resistance pathways, such as the P-glycoprotein, in this subset of patients with NK-/T- cell lymphomas leads to lower response rates.[12–14] P-glycoprotein is an ATP-dependent efflux pump, encoded by the *MDR*1 gene and the multidrug-resistance associated proteins (MRPs). This pump leads to the efflux of drugs from the cell.

The low response-rate of patients with PTCL to current therapies warrants the urgent need for alternative treatment strategies and has prompted an investigation of novel treatments. Pralatrexate is the first drug approved by the US Food and Drug Administration (FDA) specifically for the treatment of patients with relapsed or refractory PTCL. Prior to the introduction of pralatrexate into the clinic, little consensus existed on the optimal treatment for PTCL for either frontline or relapsed/refractory settings, and specific therapeutics were not available for the treatment of this disease.[7] Apart from CHOP, further chemotherapeutic options include etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (collectively known as EPOCH) and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (collectively known as hyper-CVAD).[15] During later stages of disease, relapsed patients are often treated with either a combination of ifosfamide, carboplatin and etoposide (collectively referred to as ICE), or dexamethasone, cytarabine and cisplatin (DHAP) or etoposide, methylprednisone, cytarabine and cisplatin (ESHAP). Autologous haematopoietic cell transplants are also used in advanced cases. While there has been moderate success (higher success rates associated with consolidation therapy) this treatment is plagued with a significant fraction of patients who are refractory to induction therapy. There is also a 5-year progression-free survival (PFS) and OS rates having been found to be as low as 24% and 33%, respectively.[16–18] Some positive results in the relapse setting have been observed against

certain subtypes of PTCL with the drug gemcitabine (Gemzar). Gemcitabine is a novel cytidine analogue, and is used either alone or in combination with other chemotherapeutics, namely vinorelbine (Navelbine) and doxorubicin. This regimen is known as GND. Due to the rare nature of PTCL, the majority of the literature comprises studies with small sample sizes and anecdotal case reports. Randomized trials in this patient population are scarce, and of the published series available, most are complicated to interpret due to the inclusion of heterogeneous subtypes and limited numbers of patients.

The current paper reviews literature examining the usefulness of an anti-folate drug called pralatrexate for PTCL. While pralatrexate was identified more recently in the 1990s,[25,26] folates, a family of B_9 vitamins, have been examined since the early 20th century. Folates were originally identified to be important in a number of cellular processes involved in de novo synthesis of purines and pyrimidines required for DNA and RNA synthesis and various other substrates in mammalian cells. This finding initiated the synthesis of the parental compound methotrexate in the early 1940s, where treatment of patients with methotrexate often resulted in the induction of antifolate resistance.[19,20] Hence, in the late 1970s work was initiated at the Memorial Sloan-Kettering Cancer Center in collaboration with the Southern Research Institute (SRI) aimed at rationally developing a drug that possessed greater efficacy and selectivity. The mechanism of the absorption of the natural folates in humans required efficient intestinal absorption and transport of the folates to the systemic tissues. Anti-folates such as methotrexate are highly hydrophilic and require carrier-mediated transport into tumor cells to achieve their anti-cancer activities.[21] Folates are transported into the systemic tissue primarily by the RFC, an organic phosphate antiporter.[22–24] In the mid-1990s pralatrexate, which has a very high affinity for RFC, was identified.[25,26]

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Pralatrexate ((RS)-10-propargyl-10-deazaaminopterin) is a novel 10-deazaaminopterin analogue of methotrexate consisting of a mixture of R- and S-diastereomeric folate derivatives (Fig. 1). Folate plays an essential role in cell growth and proliferation.[27] The synthetic compound folic acid is the parent structure to folate,

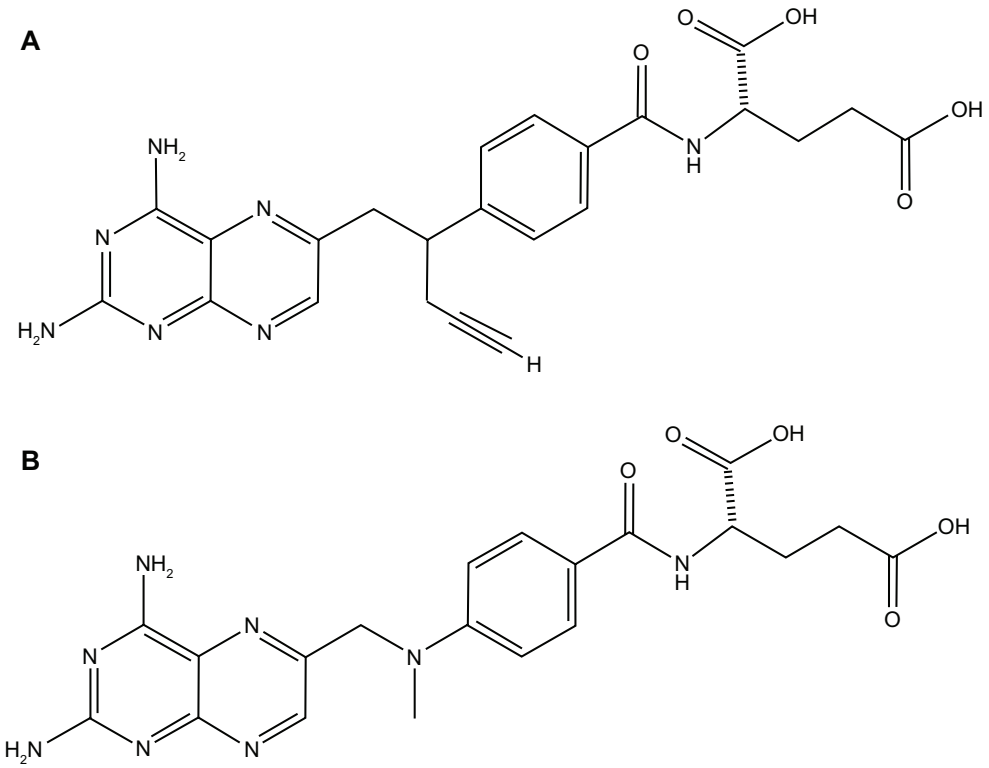

Figure 1. Chemical structures of pralatrexate (**A**) and parental antifolate analogue, methotrexate (**B**). Pralatrexate differs from methotrexate at C10, where a propargyl side chain is substituted for nitrogen with a methyl substituent.

and although not found in nature, it has been used as a source of folate to the cell due to its stability. It is also used to identify different methods of folate transport to the cells given its differing affinities to folate transporters. Within the cell, folic acid is reduced to dihydrofolate and is then subsequently converted to tetrahydrofolate (THF), both processes being mediated by dihydrofolate reductase (DHFR). After its conversion to THF, it becomes a good substrate for the enzyme FPGS. FPGS progressively polyglutamates THF into a variety of one-carbon derivatives, which each independently support specific biosynthetic reactions.[23,28] This process initiates single carbon transfer, enabling the metabolic processes involved in both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) replication to be carried out via the synthesis of purines, pyrimidines, serine and methionine.[29,30]

Antifolates are part of a group of compounds known as antimetabolites—a series of chemicals with structural similarities to naturally occurring molecules involved in DNA synthesis. In the cancerous cell, antimetabolites are disguised as normal metabolites and act primarily on DNA synthesis. The antimetabolites are most effective against actively dividing cells, and are largely cell-cycle specific. The inability of malignant cells to synthesize DNA and RNA prevents them from proliferating, eventually leading to apoptosis.[29]

In a similar manner to folate, pralatrexate enters the cell predominantly via RFC.[30,31] Pralatrexate was structurally designed to have improved cellular transport via RFC, and to undergo greater polyglutamation in comparison to methotrexate. Studies have indicated that the K_m values for RFC of pralatrexate and methotrexate are 0.3 μmol/L and 4.8 μmol/L respectively, while the V_{max}/K_m values—indicative of the rate of intracellular transport—are 12.6 for pralatrexate as compared to 0.9 for methotrexate. Therefore, the rate of influx of pralatrexate is approximately 14 times that of methotrexate.[32] Upon entry into a cell, pralatrexate is polyglutamylated by folylpolyglutamyl synthase (FPGS). This process of polyglutamylation is a key factor in antifolate-mediated cytotoxicity, and as a result of enhanced formation of polyglutamylated conjugates, there is increased intracellular drug retention.[33] Polyglutamylated products are mostly retained within the cell, and as it is a time- and concentration-dependent process, the increased intracellular half-life of pralatrexate allows for extended drug action in malignant cells. The competitive inhibition for polyglutamylation by FPGS results in the depletion of thymidine, certain purines, and other biological materials, the synthesis of which depends on single carbon transfer. This disruption to compounds necessary for DNA synthesis subsequently results in errors in DNA replication, inducing necrosis or apoptosis in rapidly dividing cells. Further, pralatrexate competitively and potently inhibits DHFR, an important enzyme in the metabolism of folate, resulting in depletion of intracellular folate stores.[29,30,34,35] It has been hypothesized that the pharmacological activity of pralatrexate is most likely through its ability to potently inhibit DHFR, demonstrating an IC_{50} value in the picomolar range.[36] Indeed, a head-to-head comparative analysis of in vitro and in vivo activities of antifolates highlighted the superior anticancer activity of pralatrexate compared to methotrexate and pemetrexed.[30] However more extensive studies involving radiolabelled pralatrexate are required to determine the reliability and efficacy of its transport kinetics.

Pralatrexate is administered to patients as an injection, known as Folotyn® (Allos Therapeutics, Inc.), through an intravenous (IV) push over 3 to 5 minutes via the side port of a free-flowing 0.9% NaCl injection IV line.[4] Administration via IV has been shown to result in complete bioavailability. The diastereomers of pralatrexate have demonstrated a steady-state volume of distribution of 105 L (S-diastereomer) and 37 L (R-diastereomer). In addition, in vitro studies have highlighted that a significant proportion of pralatrexate (approximately 67%) is bound to plasma proteins.[4] While the liver has been shown to metabolize some pralatrexate, this does not occur to significant levels. After a single dose of the drug, according to the practice undertaken in the Pralatrexate in Patients with Relapsed Or Refractory Peripheral T-cell Lymphoma (PROPEL) study, for patients with renal impairment 34% of pralatrexate was excreted unchanged in urine. Further, the mean values of systemic clearance of pralatrexate diastereomers was 417 mL/min (*S*-diastereomer) and 191 mL/min (*R*-diastereomer).[37] The terminal elimination half-life of pralatrexate is 12–18 hours (coefficient of variance (CV) = 62%–120%),[4] significantly higher than that of methotrexate. As such, increased damage to

malignant cells occurs, as the antifolate is retained within the cell for extended periods of time. Gender did not have any significant impact upon the function of pralatrexate. Furthermore, the pharmacokinetic profile of pralatrexate did not alter over successive treatment cycles, and accumulation of the drug did not occur.

Clinical Studies

Early clinical evaluation indicated the increased efficacy of pralatrexate in T-cell lymphomas as compared to B-cell lymphomas. In a phase I study comprising 4 patients with PTCL, all achieved complete remission, while conversely the 16 patients with B-cell lymphoma had stable disease at best.[31] This study was extrapolated to an additional 20 patients with relapsed or refractory PTCL, resulting in an overall response rate (ORR) of 54%–21% complete response (CR) and 23% partial response (PR), with the median duration of response being 3–26 months.[38] On the basis of the promising data from this trial, an open-label, single-group, multicentre, international clinical trial PDX 008 (PROPEL) was initiated (Table 1).

Due to the poor prognosis and high relapse rate of PTCL, following a priority review of data from PROPEL, in 2009 approval of the pralatrexate injection (Folotyn®) was granted under the US FDA accelerated approval process. Pralatrexate injection was approved as a single agent for the treatment of relapsed or refractory PTCL. PROPEL is the largest prospective study conducted in patients with relapsed or refractory PTCL, and enrolled 115 patients that had received prior therapy. These subjects were enrolled based on the Revised American Lymphoma (REAL)/WHO disease classification, where patients must have demonstrated PTCL either histologically or cytologically, as confirmed by an independent review.[4] The median number of prior systemic therapies was three; 24% had not demonstrated any response to previous therapies and 63% failed to have an objective response to the most recent prior therapy. One-hundred and nine study participants received pralatrexate (four patients did not receive pralatrexate and two treated patients failed to have eligible histology per central pathology review) at 30 mg/m^2 once weekly by intravenous push during 3–5 minutes for 6 weeks, in 7-week cycles until disease progression or unacceptable toxicity ensued.[39] The patient population comprised 68% males and 32% females, with a mean age of 57.7 years. This population was 72% white-European, 13% African American, 8% Hispanic and 5% Asian. In addition to therapy, vitamin supplementation was initiated following an analysis of patient's blood for methylmalonic acid (MMA) and homocysteine (Hcy). Patients were administered vitamin B_{12} (1 mg) intramuscularly every 8–10 weeks, as well as folic acid (1.0–1.25 mg) orally every day. In the cases where MMA level was >200 nmol/L and/or Hcy levels were >10 μmol/L, vitamin supplementation was initiated at a minimum of 10 days prior to the initial pralatrexate dose, during the first cycle.[39]

In order to assess disease status, patients received clinical examination, bone marrow examination and imaging scans. Imaging scans included computed tomography (CAT scans) or magnetic resonance imaging (MRI), and/or medical photography. These assessments were undertaken during week 7 (end of cycle 1), and subsequently at 14-week intervals. Patients who had tumor responses, when nodal-liver-spleen shrinkage met International Workshop Criteria (IWC) criteria on clinical and/or imaging scans, or those who had achieved stable disease continued to receive additional cycles until disease progression or unacceptable toxicity resulted, otherwise therapy was continually undertaken for a total of 24 months.[4]

Pralatrexate induced durable responses irrespective of age, histologic subtypes, or amount of prior therapy, including prior methotrexate and autologous stem-cell transplantation. Responses were assessed by an independent central imaging review committee,

Table 1. Two pivotal clinical trials of pralatrexate that eventually resulted in accelerated FDA approval of the drug in September 2009.

Study (year)	Phase	Patients (n)	CR	PR	ORR (%)	Median duration of response (months)
O'Connor et al[31]	I	4	4	NA	NA	NA
O'Connor et al[39]	II	115	10	20	28	9.4

using the IWC for malignant lymphoma. Specifically, results demonstrated an overall response rate of 27%; that is, the complete response, plus complete response unconfirmed, plus partial response (95% CI: 19%, 36%). Of these 27% of patients, 66% achieved this effect within the first cycle of therapy. The median duration of response was 9.4 months (ranging from 1–503 days), and 13 patients (12% of 109 evaluable patients) had a response duration of ≥14 weeks. Of these 13 individuals, six achieved a CR, one had a CR unconfirmed (CRu), and the remaining six patients had a PR.

While this study demonstrated the ability of pralatrexate to reduce tumor size, prior to its approval pralatrexate had not been shown to improve PFS or OS. The urgent need for new therapies contributed to its accelerated approval. This approval was based on the additional condition that randomized, controlled trials would be undertaken post-approval to verify and describe the clinical benefit of pralatrexate in PTCL. Currently, multi-center, randomized, phase III clinical studies are underway involving the investigation of partial or complete response to pralatrexate and survival in patients following CHOP-based chemotherapy. A two-arm, open-label, randomized, international, phase III clinical trial is also underway to evaluate the efficacy of pralatrexate compared with single-agent treatments of alisertib, gemcitabine or romidepsin as selected by the investigator in patients with relapsed or refractory peripheral T-cell lymphoma.[40]

Safety

Preliminary studies of pralatrexate in animal models highlighted that, at high concentrations, pralatrexate induced mucosal inflammation and destruction of the gastrointestinal epithelium. Multiple doses of the drug led to reversible anemia, neutropenia, and leukopenia in dogs. Furthermore, indications of hepatic toxicity were noticed—a symptom that is consistent with what is observed in human patients.[4]

Safety assessments were performed on the 111 patients in the PROPEL study who received at least one pralatrexate dose (Table 2). All of the patients enrolled in the study endured at least one adverse reaction as a result of taking pralatrexate. Mucositis (71%), thrombocytopenia (41%), nausea (41%), fatigue (36%), anemia (34%), pyrexia (34%), constipation (33%), oedema (31%), cough (29%), epistaxis (26%), vomiting (25%), neutropenia (25%), and diarrhoea (21%) were the most common adverse reactions, and were consistent with the antifolate class. Of these reactions, thrombocytopenia, mucositis, neutropenia and anemia were the most common Grade 3 or 4 reactions. The other adverse reactions were mild to moderate in severity (Table 2). Side effects from the drug also led to dose reductions in 31% of patients (most likely to 20 mg/m^2 per week), dose omission in 69% and treatment withdrawal in 23%. In total, 85% of scheduled doses were administered to those enrolled in the study.[38] Febrile neutropenia and thrombocytopenia can lead to bone marrow suppression, and therefore blood counts must be monitored while patients are taking pralatrexate. In the case of haematological toxicities, the dose should be omitted or modified. Simultaneous treatment with folic acid and vitamin B_{12}, however, should hopefully counteract these reactions, in addition to counteracting mucositis. Eight deaths were reported within 30 days of the final dose of pralatrexate—seven of these a result of progressive disease, and 1 occurring following cardiopulmonary arrest, which was possibly due to the pralatrexate.[4]

Furthermore, patients also receiving other medications, including probenecid or certain drugs that may impact relevant transporter systems—for example

Table 2. The percentage of the most common hematological and non-hematological adverse events associated with the antifolate pralatrexate in the PROPEL trial with the percentage of patients that underwent Grade 3 and Grade 4 levels of these side effects.[4,53]

Adverse effect	Incidence (%)	Grade 3 (%)	Grade 4 (%)
Non-hematologic			
Mucositis	71	18	4
Dyspnea	19	7	0
Fatigue	36	5	0
Nausea	41	4	0
Vomiting	25	2	0
Diarrhea	23	2	0
Pyrexia	34	1	1
Oedema	31	1	0
Cough	29	1	0
Hematologic			
Thrombocytopenia	41	14	19
Neutropenia	25	14	8
Amenia	34	16	2

non-steroidal anti-inflammatory drugs (NSAIDs)—require close monitoring for systemic toxicity as a result of increased drug exposure due to delayed clearance.[4] The safety, efficacy and pharmacokinetics of pralatrexate have not been evaluated in patients with renal impairment. Therefore, caution must be exercised when treating patients with moderate to severe renal function impairment. The risk for toxicity in these patients may be great due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate. Patients should be monitored during treatment for renal function and for systemic toxicity to adjust dosing accordingly; the dose should be omitted if the severity of toxicity is Grade 3 on the day of treatment. If the level of toxicity is below or equal to Grade 2 upon recovery, the dose of pralatrexate should be lowered to 20 mg/m^2. Therapy should be cancelled if is systemic toxicity elevates to Grade 4, and administration should be avoided in patients with end stage renal disease undergoing dialysis, unless the potential benefit justifies the potential risk.[41] In the case of elevated liver function test abnormalities that are ≥ Grade 3, the dose of drug must be omitted or modified. In addition, pralatrexate can cause harm to a fetus and has been classified as a Pregnancy Category D drug, due to its extreme toxicity to a developing embryo or fetus, inducing reabsorption, pre- and post-implantation loss, and decrease in weight.[4] In this regard, women should avoid pregnancy during the treatment course with pralatrexate, and for those who are already pregnant, adequate warnings are required of the risk of potential fetal harm. Nursing mothers should be advised to either discontinue nursing or discontinue the drug, taking into consideration the importance of the drug to the mother. Nevertheless, overall it was found that adverse toxicities associated with pralatrexate were manageable and reversible upon dose modification.[26,42]

Efficacy

The population of the PROPEL study included 111 patients with histologically confirmed PTCL. Of these patients, 109 were evaluable. In order to meet the inclusion criteria for this study, patients must have had relapsed or refractory disease following treatment with at least one agent, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2,[42] absolute neutrophil count (ANC) ≥ 1000/μL, platelet count ≥ 100,000/μL both at the screening point, and prior to dosing on cycle one, day one.[43] Results from the FDA review of this study highlighted that 27% (29 of 109 patients) had an observable response on a scan; however, of these patients only 13 (12%) had responses that were maintained for ≥14 weeks, 6 CR, 1 CRu, and 6PR. While pralatrexate has demonstrated increased efficacy for RFC as compared to a number of other antifolates, it is unknown as to whether this compound will cause antifolate resistance analogous to methotrexate. While methotrexate has shown to be efficacious in numerous diseases, the emergence of resistance significantly impedes its therapeutic activity. There are a plethora of mechanisms by which antifolate resistance can arise. While increased expression of the *MDR*1 protein has been associated with methotrexate-induced resistance, this seems not to be the case for pralatrexate. Studies have shown that inhibition of the *MDR*1 gene failed to restore sensitivity to pralatrexate following the acquired resistance of the antifolate.[44] Furthermore, while a correlation has been found between down-regulation in mRNA levels of RFC and pralatrexate-resistant cells, in a similar fashion to that which occurs with methotrexate, the significantly increased affinity of pralatrexate for this protein is thought to most likely result in its avoidance of this resistant mechanism.[44,45]

Patient Preference

Historically, treatment strategies for PTCL have been assessed as part of clinical studies examining the more prevalent B-cell lymphomas, accordingly resulting in poor outcomes. Treatment administered for newly diagnosed patients generally involves anthracycline-based chemotherapy regimens—mainly CHOP or CHOP-like therapy. While it has long been recognized that these conventional chemotherapeutic methods consistently provide disappointing results, with the exception of ALK-positive ALCL, this line of treatment is still considered "standard therapy".[2,46]

Chemotherapy treatment for PTCL is often undertaken in patients as part of a combination therapy or high-dose therapy, after which stem cell transplantation may be introduced. Numerous studies have shown that, in certain cases, autologous stem cell transplants are used as consolidation therapy.[47–49] For patients who have attained CR following first-line therapy, they can then undergo high-dose chemotherapy

followed by an autologous stem cell transplant. Data has shown that this is a promising approach for this subset of patients, resulting in an estimated 3-year survival rate of approximately 71%.[50] If a patient's disease progresses to relapsed or refractory stages of PTCL, pralatrexate has emerged as a standard therapeutic for this stage of disease, and is therefore introduced into treatment plans.

Place in Therapy

Given the lack of any previous therapies specifically designed for the treatment of PTCL in relapsed or refractory settings, the introduction of a novel treatment was in high demand. The FDA approval in 2009 of pralatrexate initiated a bridging of this treatment gap. While pralatrexate received accelerated approval on the basis of a single-arm phase II study, which demonstrated reduction in tumor size, the overall outcome on life expectancy was still undetermined at the point of approval. Certainly this poses inherent problems, including difficulties interpreting time-to-events endpoints such as PFS, time to progression, and OS. Additionally, the absence of any comparator arms in single-arm trials makes it challenging to realize risks or benefits associated with this drug. Even with these factors in mind, given the rarity of the disease and absence of any superior therapeutic options, the design and conduct of the PROPEL trial was under a special protocol assessment (SPA) agreement with the FDA prior to the initiation of the trial enabling its eventual acceptance into the clinic. This meant that SPA evaluated specific individual protocols, mainly in response to questions that had been raised by sponsors of the trial, in order to find whether the protocols were sufficient to reach the scientific and regulatory requirements identified by these sponsors.[4] Additionally, a series of studies have recently been undertaken exploring the possible synergy of pralatrexate in combination with other therapeutic agents in T-cell lymphoma. A study investigating pralatrexate administration together with gemcitabine in a panel of lymphoma cell lines highlighted the synergistic activity of the antifolate, as well as improved therapeutic efficacy as compared to gemcitabine in combination with methotrexate. This was achieved through significant activation of the apoptotic cascade. Additionally, this combination was superior to that of methotrexate and arabinofuranosyl cytidine (Ara-C), a therapy often administered for the treatment of lymphoproliferative malignancies.[32] The study further identified that these responses were sequence-dependent, where treatment with pralatrexate followed by gemcitabine had higher response rates than those observed when both drugs were administered simultaneously.[32] In 2011, Serova and colleagues[51] performed similar combinatorial studies with pralatrexate and a myriad of platinum drugs, antimetabolites and EGFR inhibitors, gemcitabine being amongst the tested compounds. Studies showed similar results; when pralatrexate was administered following gemcitabine, the response was additive. Following from these results, currently a phase I study involving pralatrexate and gemcitabine is underway.[52]

Conclusions

The novel antifolate pralatrexate has evolved as the first drug to be FDA approved specifically for the treatment of advanced PTCL. Rare and biologically diverse, PTCL is an aggressive disease with disparate responses to standard chemotherapeutic regimens, and subsequently has a poor prognosis. In the past, therapeutic guidelines for PTCL treatment have been largely influenced by those of B-cell lymphomas. Development of optimal therapies for PTCL is challenging due to its rarity and heterogeneity. Nevertheless, pralatrexate was synthesized in the early 1990s based on the structure of the conventional antifolate methotrexate. The rational design of pralatrexate, which has a high intrinsic affinity for RFC, results in greater internalization of the drug, predominantly in malignant cells. Further, the increased ability of pralatrexate to be polyglutamylated and retained with the cell correlates with increased tumor cell-death and improved anticancer activity. Pralatrexate is therefore a promising new drug for PTCL. Current and future studies will be aimed towards investigating additional treatment combinations with pralatrexate, in an attempt to acquire higher efficacy levels. It will be interesting to see whether there will additive or synergistic effects with other cancer therapies, as is widely anticipated.

Acknowledgements

The support of the Australian Institute of Nuclear Science and Engineering (AINSE) is acknowledged.

TCK was the recipient of AINSE awards. ALR is the recipient of Baker IDI Bright Spark top-up and Australian and AINSE post-graduate awards.

Funding Sources

Epigenomic Medicine Laboratory is supported by McCord Research. Supported in part by the Victorian Government's Operational Infrastructure Support Program. TCK and ALR declare that they have no direct financial relation with the commercial identities mentioned in this manuscript that might lead to a conflict of interest.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Author Contributions

ALR wrote the first draft of the manuscript. TCK and ALR jointly developed the structure and arguments for the paper. TCK made critical revisions and approved final version. Both authors reviewed and approved the final manuscript. KV made critical revisions and all authors approved the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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