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Preemptive Leucovorin Administration Minimizes Pralatrexate Toxicity without Sacrificing Efficacy

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Abstract

Balancing efficacy and safety of drugs is key for successful cancer therapy as adverse reactions can prohibit the use of efficacious treatments. Pralatrexate (PDX) is a novel anti-folate with a higher affinity for tumor cells than methotrexate FDA approved for use in relapsed and refractory PTCL and transformed Mycosis Fungoides (T-MF). Patients with T-MF have higher incidence of adverse events than patients with other lymphomas necessitating lower recommended dose of 15 mg/m² (vs. 30 mg/m² for PTCL). Dose-limiting (DLT) mucositis occurs in about 25% of T-MF patients, but milder mucositis is observed in almost all T-MF patients frequently leading to therapy discontinuation despite clinical response. Leucovorin rescue is standard of care for high-dose methotrexate therapy, but has not been studied or recommended for use with PDX. We report our clinical experience using leucovorin with PDX (30mg/m²) with good clinical response and no DLTs. Prophylactic leucovorin deserves further investigation in prospective clinical trials to allow patients with cutaneous lymphomas to receive full benefit of PDX therapy without intolerable toxicity.

Keywords

CTCL; Pralatrexate; Leucovorin rescue

INTRODUCTION

Optimization of chemotherapeutic regimens is one of the most important aspects of cancer therapy. Significant adverse effects may preclude the use of even the most effective therapies and management of these effects is of the utmost importance for successful outcomes. Though clinical trials uncover the majority of possible adverse events and offer insight into their management, clinical experience allows us to gain additional insight in drug administration and overall patient management.

In September of 2009, the Food and Drug Administration approved a novel folate analogue, pralatrexate (PDX) for the treatment of relapsed and refractory peripheral T-cell lymphoma (PTCL) and transformed Mycosis Fungoides (T-MF). PDX is an antifolate, like methotrexate (MTX), but compared to other antimetabolites in its class, PDX was designed

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to have a higher affinity for the reduced folate carrier-1 (RFC1) and, therefore, more selective accumulation in tumor cells.¹ Both MTX and PDX bind to and inactivate the enzyme dihydrofolate reductase (DHFR), which normally functions to maintain the intracellular folate stores, disrupting the synthesis of DNA. Folylpolylglutamate synthetase (FPGS) is an enzyme that mediates the polyglutamation of folates and antifolate agents within cells, leading to intracellular accumulation. An antifolate with enhanced affinity for either the RFC or for FPGS would result in increased intracellular retention and, thus, increased antineoplastic effects.²

Leucovorin (LV) rescue is a standard of care therapy for patients receiving high dose MTX. In contrast, current guidelines for PDX administration do not recommend that LV be administered preventatively. However, a high proportion of patients receiving PDX develop dose-dependent adverse effects that frequently represent dose limiting toxicities (DTL) and preclude therapy with this potentially beneficial drug.

In the first dedicated trial of PDX in lymphoma (phase II trial aiming to determine the maximum tolerated dose (MTD) and DTL), investigators initiated PDX at 135 mg/m²/every other day, based on a prior phase II study in non small cell lung cancer (NSCLC). However, for unknown reasons, patients with lymphoma had a much higher risk of developing mucositis and hematologic abnormalities than did patients with NSCLC. Investigators then established the MTD of 30 mg/m² weekly for 6 weeks every 7 weeks for these patients. Adverse events were managed with vitamin supplementation (folic acid and vitamin B12) and dose modifications with some improvement in symptoms. Based on these results, folic acid and vitamin B12 supplementation were recommended for all ongoing PDX studies, which did not appear to compromise the benefit of the drug, although the effect was not formally addressed.¹

The PROPEL trial, which led to the approval of PDX in relapsed PTCL, had an overall response rate of 29% at 30 mg/m² weekly for 6/7 weeks. Symptomatic mucositis was the most common treatment-related adverse event affecting more than 70% of the patients and in 22% of the cases it was the DLT; gastrointestinal side effects were also common affecting nearly 50% of all patients; hematologic toxicity was dose limiting in more than 30%. These adverse events were not, therefore, prevented by administration of vitamin B12 and daily folic acid.³ In Cutaneous T-cell Lymphoma (CTCL) the maximum tolerated dose (MTD) was even lower, 15 mg/m² weekly for 3 of every 4 weeks. CTCL patients had higher incidence of DLT on 30 mg/m² with a majority of patients experiencing severe mucositis.⁴

In clinical practice, nearly all of our CTCL patients develop mucositis even on lower 15 mg/m² weekly dosing, frequently precluding administration of the drug even in cases of clinical response. We have used LV preemptively in patients with advanced progressive CTCL requiring higher than FDA-approved dose of PDX (30mg/m²) and have eliminated or alleviated severe adverse events while achieving significant clinical response to the drug. Considering our early experiences, PDX-LV combination merits evaluation in prospective clinical trials to formally assess its safety and efficacy.

CASE SERIES

We present three initial cases, whom we treated using LV preemptively and observed clinical responses.

The first patient was a 42-year old African-American female with 6 year history of CTCL, who progressed from patch/plaque MF to Sezary syndrome with lymphadenopathy (LAD) and bone marrow involvement, and developed CD30+ tumors with large cell transformation. Her disease progressed rapidly despite aggressive therapies, including bexarotene, denileukin diftitox, localized and total skin electron beam, romidepsin, gemcitabine, and several cycles of CHOP. She was eventually admitted to the hospital with generalized LAD, thick erythroderma, numerous ulcerated cutaneous tumors, urinary retention, bacteremia, skin abscesses, severe pain and inability to ambulate. She received 30 mg/m² PDX followed by one dose of 50 mg intravenous LV infusion 24 hours later in 8 weekly doses with one week of rest per cycle for palliation. Clinical response was observed after the first infusion and continued throughout the treatment course. She did not have mucositis or significant hematologic abnormalities and reported only mild fatigue. She achieved a significant partial response with resolution of LAD (Figure 1), cutaneous tumors and 80% improvement in erythroderma (Figure 2), which lasted for 3 months. Unfortunately, at that time she contracted H1N1 influenza leading to respiratory failure and death.

The second patient was a 78-year old Caucasian male who presented to us with a 1.5 year history of a single 10×10 cm grade 3, progressively worsening ulcer with thick exophytic borders on his left ankle. A biopsy of the border was consistent with MF. On follow up 3 weeks later, he was found to have hundreds of new draining and malodorous tumors on the face, trunk and extremities. Biopsy of these new lesions revealed large cell transformation. PET/CT showed no evidence of systemic disease. He was initially treated with a combination of oral bexarotene, romidepsin and electron beam that resulted in near complete resolution of his disease within three months. He had a decline in status due to dehydration, weight loss, nausea and anemia which led to discontinuation of therapy and relapse within one month. Palliative care and therapeutic options were discussed and PDX with LV rescue was chosen by the patient and the family.

PDX 30 mg/m² followed by a single 50 mg intravenous LV infusion 24 hours later was initiated in 6 weekly doses with one week of rest per 7 week cycle. He also received local electron beam to his groin with complete resolution of his tumors within one cycle. He had no mucositis or other serious adverse reactions. He has received 5 full courses of PDX + LV rescue with maintenance of his response for 9 months.

The third patient was an 80-year old Caucasian female diagnosed with Sezary syndrome in 2009 after a 3–4 year history of eczema. Upon presentation to our clinic in 2010, she had been on several courses of corticosteroids with temporary improvements and had failed treatment with vorinostat. After discussion of various therapies she opted to enroll into a clinical trial evaluating combination of PDX with bexarotene. She received PDX at 15 mg/m² given weekly for 3 out of 4 weeks per cycle plus 150mg/m² of daily oral bexarotene. She had a partial response to treatment but began developing mucositis during her third

cycle and eventually had to be withdrawn from the trial due to sustained grade 2 oral mucositis and ulcerations of the nasal mucosa, axilla and medial buttocks resulting in a decline in her quality of life. She could not afford prescription medications, including bexarotene. Her disease progressed despite therapy with extracorporeal photopheresis. Because of her known response to PDX in the past, we decided to repeat the therapy with LV rescue after discussion with the patient. Because of disease progression a higher dose of PDX (30 mg/m²) was chosen to be given in 7-week cycles. She tolerated treatment well and had no episodes of mucositis or other significant side effects.

In light of mixed response after 4 infusions of PDX within the first cycle, her LV was changed from 50 mg IV to 15 mg PO, administered 24 hours after PDX. Low dose oral bexarotene 150 mg/m² was added for potential synergy. After only 2 weeks of this regimen, she had significant improvement of her disease and experienced no mucositis or other significant adverse events.

DISCUSSION

Pralatrexate is a new generation designer antifolate, which has been suggested to be a more potent antineoplastic agent than MTX but with similar toxicity.⁵ In contrast to MTX, current guidelines do not recommend preemptive use of LV for PDX. LV is presently recommended only for PDX overdose and can be used to treat significant adverse events reactively.⁶ However, vast majority of patients develop at least one grade 2 adverse event; up to 30% of patients experience DLT, necessitating dose reduction and consequently compromising clinical outcomes.

To develop an optimal administration schedule of antifolate and LV for a specific cancer, understanding of its intracellular pharmacokinetics is vital. Unfortunately, very little is known about intracellular half-life of LV. We have studied clinical and pharmacological literature extensively to understand what the optimal regimen for PDX with LV rescue should be in order to preserve its efficacy and to minimize toxicity.

The use of LV rescue for antifolates toxicity is controversial. Studies have demonstrated decreased efficacy of MTX (response rate 17.2% versus 36.7%) in locally advanced and recurrent squamous cell cancer of the head and neck⁷ and of edatrexate (response rate 16% versus 25%) in patients with mesothelioma⁸ when 10 mg/m² IV or 15 mg orally of LV every 6 hours in 4 doses was given 24 hours after weekly standard dosing of the drug. While mitigating antifolate toxicity, these studies raised concern about maintaining efficacy of the drugs. However, LV was also evaluated in clinical trials of patients with various cancers⁹ and with NSCLC¹⁰ treated with another antifolate, pemetrexed. Response and toxicity were not broken down by LV rescue, but its administration did not appear to compromise efficacy.

Another study, which allowed longer wash out period of LV prior to administration of standard dose of edatrexate for the treatment of NSCLC, showed the overall response rate to be comparable in both groups (47% in standard vs. 43% in LV group). The LV group had 33% grade 2 stomatitis or higher versus 77% in the standard group. In addition, the average

edatrexate dose delivered per cycle was higher in the LV group (111 mg/m² vs. 136 mg/m²).¹¹ In an abstract published in 2011, Haddad et al. evaluated the efficacy of short oral LV rescue (SOLR) in PDX induced mucositis in patients with PTCL. Oral LV was given reactively to patients who had refractory mucositis despite dose reduction or omission who would otherwise have to stop the medication. The subsequent dose of PDX was not given until at least 2 days after the last dose of LV. All patients had complete resolution of mucositis by day 7, allowing for continuation of planned PDX therapy. Most notably, none of the patients lost their response to PDX on this regimen.¹² The outcomes of these four studies suggest that LV does not affect the efficacy of antifolate therapy if adequate time is provided between the last dose of LV and the subsequent antifolate dose.

The timing of LV dosing appears to play a critical role in both the mitigation of toxicity and the impact on efficacy of antifolates. The initiation of LV rescue for MTX is often determined by its plasma levels. Because the proposed mechanism of toxicity lies within the prolonged intracellular retention of PDX, plasma PDX levels may be less relevant in the decision to initiate LV rescue.

The possible decreased efficacy of antifolates after LV administration is related to LV's intracellular accumulation. LV is particularly difficult to study because its intracellular accumulation and elimination is affected by a number of factors: it varies between different tissues (e.g. solid tumors vs. hematological malignancies), the amount of an active isomer present, timing and dosing as related to antifolate administration, among other things.¹³ Based on our investigation of clinical pharmacology, we concluded that a minimum time for LV “wash out” is necessary to minimize the possibility of decreased efficacy of the subsequent antifolate dose. Considering the terminal half-life of LV is approximately 6 hours for both intravenous and oral administration, a minimum of 2 days is required for elimination for the biologically active isomer from the plasma.¹⁴

We evaluated the previously reported data on the use of LV in antifolate therapy, its potential for efficacy compromise, and the clinical pharmacology of LV to create a treatment regimen for end-stage CTCL patients with limited therapeutic options.

We have successfully used LV preemptively in end-stage CTCL patients 24 hours following administration of PDX, allowing for 6 days wash out period between PDX dosages. We have observed clinical response to PDX without usual dose limiting side effects. Future randomized prospective clinical trials are needed to optimize PDX-LV use for therapy of CTCL and other malignancies.

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