Case study: Leucovorin support to minimise mucositis in Pralatrexate therapy

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Introduction

Peripheral T-cell lymphomas (PTCL), such as angioimmunoblastic T-cell lymphoma (AITL), are generally aggressive neoplasms that approximate to 15 percent of all non-Hodgkins lymphomas in adults.

Most patients treated for PTCL will relapse or develop refractory disease, with meta-analysis reporting a 37 percent five-year overall survival in PTCL patients treated with standard chemotherapy.[1]

Pralatrexate is a novel antifolate compound approved for the treatment of relapsed or refractory peripheral T-cell lymphomas. The recommended dosing schedule is 30mg/m^2 on day 1, 8, 15, 22, 29, 36 every cycle of 49 days. Other than haematological toxicity, its predominant dose limiting toxicity is mucositis, with incidences of up to 71% among patients.[2]

Leucovorin (calcium folinate) has been reported to reduce mucositis without compromising efficacy. The strategy adopted at Colombia University, the Colombia Regimen, 15mg orally twice a day from day three to six, has been reported to be effective.[3]

Figure 1: Pralatrexate (FOLOTYN®) as listed on the PBS from April 1st, 2018.

Objective

To present a case where leucovorin dramatically reduced the severity of mucositis and prevented future recurrences of mucositis in a patient receiving pralatrexate for the treatment of relapsed angioimmunoblastic T-cell lymphoma.

Case Background

Our patient is an 85-year-old male with relapsed AITL and a history of immune thrombocytopenia purpura.

Previously treated with six cycles of mini-CHOP, he was considered unsuitable for salvage chemotherapy.

He was commenced on pralatrexate on December 28th, 2018.

Due to frailty and concerns with tolerability, he was started on a reduced dose of 20mg/m^2.

Case Progress and Outcomes

1 week prior
- Patient admitted with relapsed AITL
- Commenced Vitamin B12 1mg IM and Folic Acid 1mg PO daily

28 Dec 19
- Commenced Cycle 1 Day 1 Pralatrexate 37mg *(20mg/m2)*
- Dose reduction due to frailty
- Weight 71.9kg
- Body Surface Area (BSA): 1.83m^2

4 Jan 19
- Cycle 1 Day 8 Pralatrexate 37mg *(20mg/m2)* given
- Patient discharged home

8 Jan 19
- Presented to ED with grade 4 mucositis and thrombocytopenia (plt 27) with associated epistaxis and lethargy
- Severe oral pain limiting oral intake
- Treated with Peter Mac mouthwash, topical lignocaine viscous

23 Jan 19
- Delayed by 9 days
- Dose reduction required
- Cycle 1 Day 15 Pralatrexate 27.5mg *(15mg/m2)* given

30 Jan 19
- Cycle 1 Day 22 Pralatrexate 27.5mg *(15mg/m2)* given

4 Feb 19
- Presented to hospital with sepsis (non-neutropenic)

18 Feb 19
- Delayed by 12 days
- Cycle 1 Day 29 Pralatrexate 27.5mg *(15mg/m2)* given
- Weight: 68.5kg (4.7% weight loss)

25 Feb 19
- Cycle 1 Day 36 Pralatrexate 27.5mg *(15mg/m2)* given

14 March 19
- Dose reduction due to residual mucositis
- Cycle 2 Day 1 Pralatrexate 18mg *(10mg/m2)* given
- Weight 62.3kg (13% weight loss), new BSA: 1.7m^2
- **Added Leucovorin 15mg BD from Day 3 - Day 6**

21 March 19
- Trialled increasing to Cycle 2 Day 8 Pralatrexate 26mg *(15mg/m2),* tolerating dose

March – May
- 5 doses given of Pralatrexate 26mg *(15mg/m2)*
- Leucovorin **withheld** for Cycle 2 Day 22 & Cycle 2 Day 29 Pralatrexate due to high eosinophils

16 May 19
- Further dose reduction due to ongoing mucositis
- Cycle 3 Day 15 Pralatrexate 17mg *(10mg/m2)* given + Leucovorin 15mg BD from Day 3 - Day 6
- Weight 56.5kg (21% weight loss)

May – present (Oct 19)
- **Patient has continued on the same dose + Leucovorin**
- **No recurrence of mucositis**
- **Weight gain (as of 10/10/19: 64.4kg)**

Discussion and Conclusion

Pralatrexate, as one of the first new drugs approved for patients with relapsed or refractory TCL, has already had a significant impact on the disease, with several experiences to establish its optimum use, including that leucovorin can reduce much of the risk of mucositis.

Before leucovorin was incorporated into our patient's treatment, he experienced grade 4 mucositis and thrombocytopenia within two weeks of treatment, requiring hospital admission for management. The severity of mucositis also contributed to significant weight loss, at one point a reduction of 21% from baseline weight.

Mucositis not only significantly impacts a patient's wellbeing but also dosing continuity. After leucovorin was added, our patient was able to tolerate pralatrexate with less interruption. Notably, our patient experienced ongoing mucositis when leucovorin was withheld for two consecutive doses as it was thought to have contributed to eosinophilia.

Our patient's PET scan post cycle one showed good metabolic response but some residual disease. Due to this as well as mucositis with higher doses of pralatrexate, our patient was maintained on 10mg/m^2 with leucovorin support from cycle two onwards with no plans to dose escalate. This response further highlights the importance of maintaining the dosing schedule.

When our patient commenced pralatrexate in , there were no official recommendations on strategies to reduce toxicity, nor any guidelines for the optimal dosing of leucovorin. Since then, eviQ, the Australian resource for cancer treatment protocols have updated their Peripheral T-cell lymphoma pralatrexate protocol to include leucovorin to the treatment schedule. This is based on preliminary data from a phase II trial demonstrating a reduction in the rate and grade of mucositis. In the trial, leucovorin was administered for 2 consecutive days beginning 24 hours after each dose of pralatrexate, 25mg three times a day.[4] Due to the tablet strength availability in Australia, eviQ recommends 30mg in its protocol.

Incorporating leucovorin into our patient's pralatrexate therapy reduced the severity of his mucositis and enabled him to continue treatment, which is important in such rare diseases where treatment options are limited.

References

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