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The Addition of Low Dose Acetazolamide as an adjunct in patients undergoing High dose Methotrexate is safe and beneficial

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Acknowledgment and Authorship

Matthew Ku (first author) - designed the study, performed the data collection, analysed the data, and wrote the paper. Ali Bazargan - contributed to the collection of data and its analysis, and

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assisted in editing the paper. Constantine Tam (final author) - assisted in designing the study and contributed to the collection of data. analysed the data, and assisted in editing the paper.

All the authors have no conflict of interest to declare

Abstract

Background: High-dose methotrexate (HDMTx) is utilised in central nervous system (CNS) lymphoma and acute lymphoblastic leukemia (ALL) due to its ability to penetrate the blood-brain barrier. Despite its efficacy, nephrotoxicity is a potentially serious toxicity that could also exacerbate other methotrexate related toxicities and compromise dose intensity. Acetazolamide (AZL) is a carbonic anhydrase inhibitor that causes an increase in bicarbonate excretion and consequently urine alkalinisation. Following occurrences of HDMTx induced acute kidney injury (AKI) due to inadequate urine alkalinisation at our institution, routine AZL was administered to appropriate patients from 2010 onwards. *Aim:* Given inadequate urinary alkalinisation is the major risk factor for MTx crystal precipitation and prolonged excretion, the addition of AZL to the routine renoprotective measures was analysed. In addition, since fluid overload is a common consequence of HDMTx treatment, the effect of AZL on fluid balance was also examined. *Methods:* This is a retrospective, single-centred cohort study examining the mitigation of HDMTx induced toxicities by AZL in 92 patients over a 6 year period. *Results:* AZL showed a strong trend of preventing either AKI (as per CTCAE version 4.03) or delayed MTx elimination (>5 days), especially in males. Furthermore, AZL also resulted in reduced weight gain and fewer episodes of urinary pH<7.0. *Conclusion:* AZL appeared to diminish the incidence of HDMTx induced toxicities, including reducing oedema related weight gain. With mild, preventable hypokalaemia as the only noteworthy toxicity, AZL could be considered as an adjunct to HDMTx patient care.

Introduction

Methotrexate and its use in haematological malignancies:

Methotrexate (MTx) is an antimetabolite and a folic acid antagonist that binds to the catalytic site of dihydrofolate reductase (DHFR) ^[1]. It interferes with the synthesis of DNA, RNA and some key proteins. It is extensively used in the treatment of haematological cancers, particularly at high doses (ie >1g/m²) in central nervous system (CNS) lymphoma and acute lymphoblastic leukaemia (ALL).

High dose methotrexate (HDMTx) is widely accepted as the most effective anticancer drug for either upfront or relapsed CNS lymphoma^[2-4]. An important reason is its ability to penetrate the blood-brain barrier, a hurdle that many chemotherapy agents cannot overcome. CNS lymphomas are rare and aggressive lymphoid neoplasms that are predominantly of B cell origin^[5]. They account for about 4% of all brain cancers^[6], and despite initial response to treatment, the majority recur^[7]. HDMTx containing regimens have been shown to increase patient survival^[8-15], especially in combination with high dose cytarabine^[4, 16, 17] or with whole brain radiotherapy^[9, 18, 19]. The antitumor effect of HDMTx in the CNS is correlated with doses above 3g/m² ^[20, 21]. Furthermore, adequate MTx levels in the cerebrospinal fluid (CSF) also require rapid infusion, with three or four hours suggested as the optimal duration^[5, 6, 22, 23]. HDMTx is also used, either intravenously or intrathecally, to prevent secondary CNS lymphoma from relapse of high risk systemic NHL (HR-NHL), such as testicular DLBCL^[24-29]. CNS relapse occurs in about 5% of patients with DLBCL and portends a poor prognosis^[28]. CNS prophylaxis has been shown to reduce the incidence of CNS-related events^[25]. Similarly, HDMTx

is also utilised in ALL treatment, as it crosses the blood-brain barrier to eradicate leukemic cells from CNS. Moreover, HDMTx not only prevents CNS recurrence but also haematologic relapses^[30].

Adverse effects related to HDMTx therapy include mucositis, hepatotoxicity, nephrotoxicity and fluid overload. HDMTx therapy is characterised by a highly variable pharmacokinetic behaviour, due to its elimination renally and potential for drug interactions^[17]. HDMTx-induced acute kidney injury (AKI) is a rare but life-threatening complication^[31]. The overall incidence rate of HDMTx-induced AKI is approximately 1.8% (range, 0%-12%). HDMTx-induced AKI can range from asymptomatic increase of the serum creatinine (sCr) solely to more serious AKI. HDMTx-induced AKI can also increase the risk of other MTx related toxicities^[32]. Furthermore, subsequent MTx doses are often reduced due to nephrotoxicity^[6, 33]. Hence minimising MTx induced AKI will permit optimal MTx therapy^[34].

HDMTx-induced AKI is attributed to tubular obstruction due to the precipitation of MTx and its metabolite (crystal nephropathy), which may be exacerbated by low urinary pH and reduced tubular flow due to hypovolemia^[32]. MTx and its metabolites are poorly soluble under acidic urinary pH, hence the routine practice of urine alkalinisation, folinic acid rescue, and adequate intravenous hydration prior to, during, and after the administration of HDMTx to assist in renal excretion^[35]. MTx may also have a direct effect on the renal tubules^[34].

Acetazolamide and HDMTx:

Acetazolamide (AZL) is a carbonic anhydrase inhibitor. In the renal proximal convoluted tubule it acts by blocking carbonic anhydrase, causing amongst many effects, an increase in bicarbonate excretion and consequently urine alkalinisation^[36]. Urinary alkalinisation can occur within 30 minutes, and persists for 12 hours^[1]. A study by Shamash and colleagues found that AZL 500 mg QID effectively alkalinised the urine in patients treated with HDMTx, and plasma MTx levels fell satisfactorily at 24 and 48 hrs. They concluded that AZL is an effective method of achieving urinary alkalinisation in HDMTx therapy^[37].

Following the observation of HDMTx induced AKI, delayed MTX excretion and fluid overload in our patients, routine AZL was commenced for the appropriate patients from 2010 onwards. A lower

dose of 250mg TDS was administered because the initial higher dose had caused more severe hypokalaemia. There was also potential interaction between acetazolamide and sodium bicarbonate.

This is a single centre, retrospective cohort study examining the use of AZL in patients receiving HDMTx for haematological malignancies. Patients that had received AZL were compared to those that had not. Our experience suggests a reduction in the incidence of HDMTx induced toxicities such as AKI and fluid overload, and that AZL could be used to ameliorate the adverse effects of HDMTx.

Methods

Patient Data Collection

Data of patients who have had HDMTx therapy for a haematological malignancy at our institution between 2007 and 2013 were collected. HDMTx was defined as MTx $>1\text{g}/\text{m}^2$. Consecutive patients were identified through pharmacy records and their charts were reviewed to determine if they had (1) AKI/nephrotoxicity (\geq Grade 2 serum creatinine rise according to CTCAE version 4.03), (2) delayed MTX elimination (≥ 5 days for MTx level to be ≤ 0.05 $\mu\text{mol}/\text{L}$) or other complications including fluid overload and weight gain, and (3) whether AZL had been administered. Apart from AZL, the routine care and management of HDMTx therapy did not differ between the two groups. At our institution some patients treated with MTx started receiving AZL in 2010, according to the discretion of their clinician. We compared the characteristics and the outcomes of patients who received AZL with those who did not. Data management and analysis were conducted in accordance with the National Health and Medical Research Council Act 1992, the National Statement on Ethical Conduct in Human Research 2007 (updated May 2015), and the Helsinki Declaration of 1975, revised in 1983 and 2000.

Statistical analysis

Categorical and continuous variables were compared using Chi-square / Fisher exact and Mann-Whitney tests, as appropriate. All p-values are two-sided, with $p < 0.05$ taken as being statistically significant; no adjustments were made for multiple comparisons.

Results

Patient demographics

In total, 92 patients were administered HDMTx for their malignancies, resulting in 263 cycles of HDMTx. 34 (37%) patients were female and 58 (63%) were male, equating to 98 (37.3%) and 165 (62.7%) cycles of HDMTx respectively. The majority of patients were older, with 62 (67.4%) patients over 50 years of age and 30 (32.6%) under 50 years old. Based on the Eastern Cooperative Oncology Group (ECOG) performance status criteria, most of the patients had ECOG score of 0 (61 patients; 66.3%), with 15 patients (16.3%), 11 patients (12%), and 5 patients (5.4%) having ECOG scores of 1, 2 and 3 respectively. The majority of patients were diagnosed with either PCNSL (36/92, 39.1%) or HR-NHL (30/92, 32.6%). A substantial number of patients were treated for ALL (18/92, 19.6%). Patient demographics are summarised in Table 1. An AKI was defined as \geq Grade 2 serum creatinine rise according to CTCAE version 4.03. Out of 263 cycles of therapy, 236 cycles had adequate analysable data and were analysed individually. Some patients who initially did not receive AZL were administered AZL in subsequent cycles due to renal impairment, and these cycles were analysed separately.

The AZL group and non-AZL group were comparable in baseline patient and disease characteristics

The salient variables with potential impact on the incidence of HDMTx induced AKI were examined. These were age, gender, ECOG, and other potential nephrotoxic factors during treatment. These factors included pre-existing comorbidities such as diabetes mellitus and glomerulonephritis, as well as medications such as diuretics and ACE inhibitors. The AZL group and the non-AZL group were not significantly different, with the exception of the AZL group having a higher proportion of older (>50 yo) male patients and more patients with poor ECOG status (Table 1). The non-AZL group had a slightly higher proportion of patients with nephrotoxic factors. Overall, 85/236 (36%) cycles of HDMTx were associated with concomitant AZL.

AZL showed a trend in the prevention of either AKI or prolonged MTx elimination

As expected, HDMTx induced AKI was significantly correlated with delayed MTx elimination (mean 6.5 days for AKI versus 4.0 days for non-AKI, $p=0.001$). Furthermore, male gender was found to be a risk factor for HDMTx induced AKI (Fig 1).

AZL showed a strong trend in preventing either AKI (\geq Grade 2 sCr increase as per CTCAE version 4.03) or delayed MTx elimination (defined as >5 days). AKI or delayed MTx elimination occurred in 24/164 (14.6%) of the non-AZL group, versus 4/68 (5.9%) of the AZL group ($p=0.063$) (Fig 2). This was exemplified by Fig 3, which is a graph of a patient's serial creatinine levels (sCr) in 4 cycles of HDMTx. He was found to have a much higher sCr without AZL initially, and then completed 3 further cycles of HD-MTX without creatinine rise under AZL cover.

The beneficial effects of AZL on HDMTx induced AKI or delayed MTx elimination appeared to be predominantly in males and not in females. In the non-AZL group, 4/64 (6.3%) females had either AKI or delayed MTx elimination, versus 20/100 (20%) males ($p=0.015$). AZL seemed to have abolished this gender disadvantage, with 2/29 (6.9%) females and 2/39 (5.1%) males having either AKI or delayed elimination, respectively ($p=0.759$).

AZL use resulted in significantly less weight gain and effective alkalinisation of urine, and was well tolerated

Being a diuretic, it was not surprising that AZL usage was associated with significantly less weight gain, a common issue associated with hyperhydration during HDMTx treatment. The median weight gain was 3.0kg (range 0 - 13, $n=151$) in the non-AZL group, compared to 1.0kg (0 - 6, $n=85$) in the AZL group ($p<0.001$) (Fig 4). Moreover, urinary alkalinisation was also more effective with the use of AZL. 40/150 (26.6%) in the non-AZL group had at least one episode of urinary $\text{pH}<7.0$, compared to 10/86 (11.6%) in the AZL group ($p=0.029$) (Fig 5).

Finally, AZL was well tolerated by our patients, with mild hypokalaemia being the only common complication (48.5% of AZL group). This adverse effect was preventable by the introduction of

routine oral potassium supplementation.

Discussion

HDMTx is considered the gold standard in the treatment of CNS lymphoma. It is also a mainstay in the prevention of CNS disease in high risk NHL and ALL. Given that it is one of the very few chemotherapeutic agents that are capable of penetrating the blood-brain barrier, its utilisation in these diseases is expected to increase in the future. One of HDMTx induced toxicities is AKI, which can lead to increased mucosal and marrow toxicity. Hence, it is crucial to minimise its occurrence. A previous study by Shamash and colleagues showed that acetazolamide (AZL) at a high dose of 500mg QID was an effective method of achieving urinary alkalinisation in HDMTx therapy[37]. This led to our hypothesis that AZL could reduce the incidence of HDMTx induced AKI, and in turn, other toxicities.

This is a retrospective, single-centred cohort study examining the use of AZL as an adjunct during HDMTx therapy. Over the 6 year period between 2007 and 2013, 92 patients with various different lymphoid malignancies were treated with HDMTx, with AZL introduced as an adjunct in 2010. The patients that had received AZL had similar demographic characteristics as those that did not, with the exception of a higher proportion of AZL group being over the age of 50 or of a worse ECOG score. This most likely reflected a tendency by the clinicians to administer AZL to an older, more frail patient cohort in an attempt to reduce the risk of toxicities. Nonetheless, this bias would further strengthen the significance of the data as one would expect a higher incidence of toxicity in the AZL group. On the contrary, although not quite reaching statistical significance, AZL group showed a strong trend of preventing either AKI or delayed MTx elimination (defined as >5 days). This was especially applicable to the male cohort, which appeared to be more vulnerable to these complications. Furthermore, AZL group also demonstrated reduced weight gain and fewer episodes of urinary pH<7.0. These results indicated the usefulness of concomitant administration of AZL in HDMTx; not only does it appear to diminish the incidence of AKI or delayed elimination, thus ameliorating toxicity and preventing longer hospital stays, but it also improves patient comfort by

reducing oedema related weight gain. With mild, preventable hypokalaemia as the only noteworthy toxicity of AZL, it is an affordable therapy that is uncomplicated to administer.

Conclusion

In conclusion, this retrospective cohort study demonstrated that AZL could be used as an adjunct treatment in HDMTx regimens. Given that it is relatively cheap and easy to administer, it could be considered as a standard addition to HDMTx patient care.

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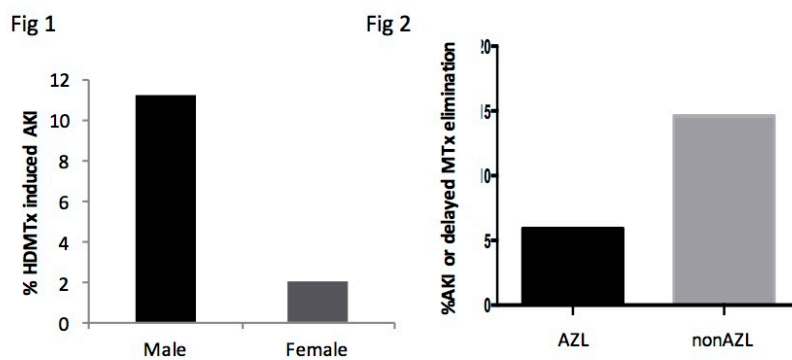


Fig 1. Male subjects have a higher incidence of HDMTx induced AKI compared to the female subjects. Fig 2. AZL showed a strong trend in preventing either acute kidney injury (AKI; \geq Grade 2 sCR increase as per CTCAE version 4.03) or delayed MTx elimination (defined as >5 days). p= 0.063

Fig 3

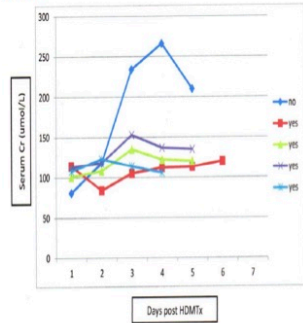


Fig 4

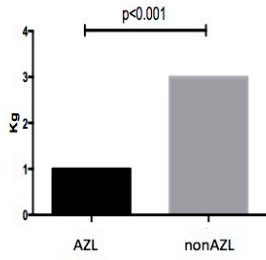


Fig 5

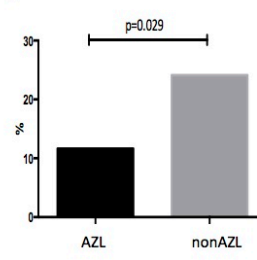


Fig 3. A graph of a patient's sCr in 4 cycles of HDMTx, depicting much higher sCr without AZL (top line) versus sCr levels with AZL in subsequent cycles. Fig 4. AZL usage was associated with significantly less weight gain, as the weight increase on non-AZL group was almost 3 times the weight gain of the AZL group. Fig 5. Frequency of urinary acidification (urine pH<7.0) was reduced with the use of AZL.

Tables and Figures

	AZL gp	Non-AZL gp	p value
Gender (n=92 pts)			
Male	55.3%	51.9%	0.25
Female	44.7%	48.1%	0.12
Age >50yo (n=92 pts)	81.6%	57.5%	0.026
Age >70yo	26.3%	22.2%	0.098
Age range	19-84yo	19-80yo	
ECOG (n=92 pts)			
0-2	92.1%	96.3%	0.093
3-4	7.9%	3.7%	0.043
Disease type (n=92 pts)			
Primary CNS NHL	38.1%	40.1%	0.19
NHL	32.2%	33%	0.52
ALL	10%	9.6%	0.43
Dose of MTx (n=236 cycles)			
Median dose	5.37g	4.2g	0.11
Quick infusion (2-4hrs)	61%	44.1%	0.042
(n=236 cycles)			
Baseline elevated serum creatinine (all grade 1)	7.9%	9.3%	0.32
Presence of potentially nephrotoxic factors*	50%	55%	0.47

*Nephrotoxic factors included 1. drugs including ACE inhibitors, Angiotensin receptor blockers, cyclosporin, diuretics, some antibiotics (eg gentamicin), NSAIDs. 2. comorbidities such as diabetes mellitus and glomerulonephritis

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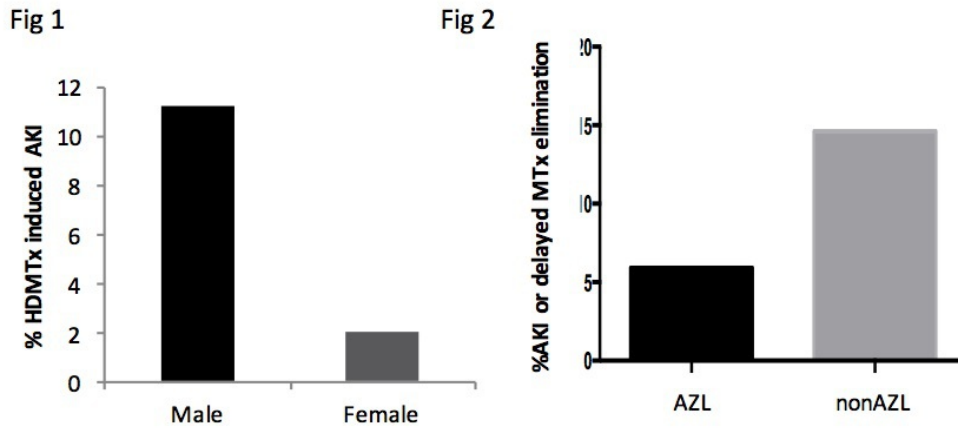


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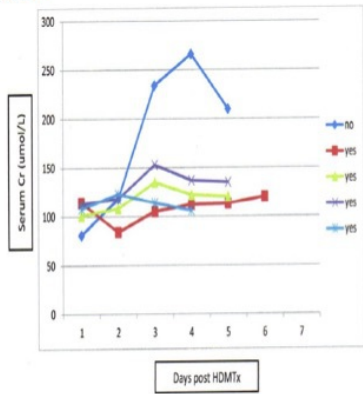


Fig 4

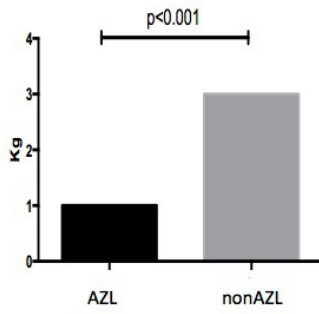


Fig 5

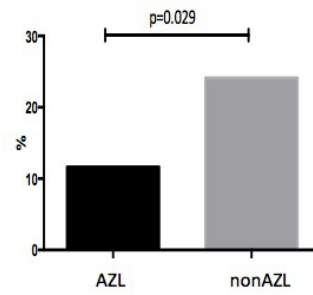


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