A single centre experience of using ciclosporin and mycophenolate mofetil immunosuppression in relapsed/refractory angio-immunoblastic T cell lymphoma.

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INTRODUCTION

Angio-immunoblastic T cell lymphoma (AITL) has a poor prognosis with overall survival of 5.5 months in transplant-ineligible relapsed-refractory disease. The 2016 WHO Classification classes AITL as a nodal T cell lymphoma. AITL is more common with increasing age. Median age at presentation of 65 years[1]. This limits intensive treatment options in less fit patients.

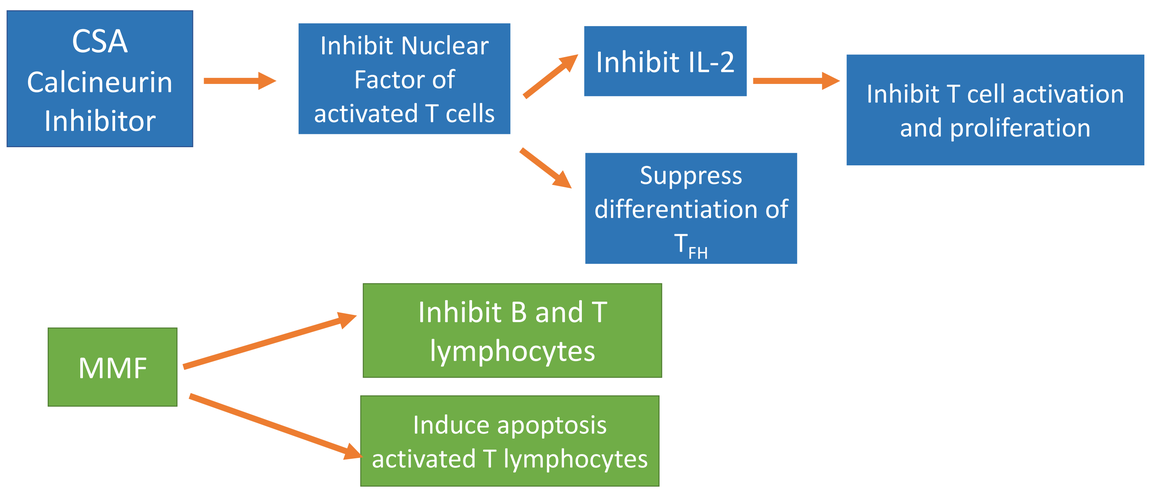
AITL is characterised by immune dysregulation. Immunosuppressants are thought to have an immunomodulatory effect. We describe 3 cases of relapsed/refractory AITL with long remissions following treatment with ciclosporin and mycophenolate mofetil.

IMMUNE DYSREGULATION

Immune dysregulation distinguishes AITL from other mature T cell lymphomas. T follicular helper cells (T_{FH}) cells are implicated in AITL. These effector T cells regulate B cell activation and differentiation within the germinal centre. Dysfunctional T_{FH} cells lead to loss of immune tolerance, manifesting in autoimmune disease as well as malignancy.

Ciclosporin and mycophenolate mofetil are immunosuppressive agents. Suggested mechanisms for ciclosporin in AITL are by inhibiting T cell activation and T_{FH} differentiation. Mycophenolate suppresses both B and T cell proliferation.

Fig 1: Mechanism of CSA and MMF



Case 1

- A 45-year-old with Stage 3 disease presenting with bilateral neck swelling and weight loss completed 6 cycles of CHOP, achieving a Deauville 3 response on end-of-treatment PET-CT.
- He progressed at 29 months and failed to respond to 3 lines of salvage therapy (alternating IVE and methotrexate, single agent lenalidomide followed by cisplatin with gemcitabine).
- He was commenced on ciclosporin 250mg twice daily, achieving a complete response, facilitating allogeneic stem cell transplantation.
- Ciclosporin was discontinued 5 months post-transplant and he continues in remission 55 months later.

Case 2

- A 71-year-old with Stage 4B disease presented with rash, lethargy and supraclavicular lymphadenopathy. Staging confirmed bone marrow infiltration and bowel involvement.
- She was treated with CHOP and prophylactic intrathecal methotrexate as first line treatment.
- Despite metabolic remission on end-of-treatment PET-CT, she re-presented with a rash and florid lymphadenopathy 5 weeks later.
- She was unable to proceed with intensive salvage therapy due to poor performance status and was commenced on ciclosporin. Shortly after starting ciclosporin, she developed ciclosporin induced haemolytic anaemia.
- She was switched to mycophenolate mofetil 750mg twice daily, initially combined with 4 cycles of rituximab and IVIG.
- PET-CT at 8 and 13 months showed complete metabolic remission. Response is currently sustained at 26 months.

CASE 3

- A 65-year-old with Stage 3A disease presented with a blistering polymorphic rash and cervical lymphadenopathy. She was treated with 6 cycles CHOP on clinical trial.
- End-of-treatment PET-CT confirmed refractory disease and she soon developed autoimmune haemolytic anaemia.
- She was salvaged with IVE and intermediate dose methotrexate, followed by consolidation with autologous stem cell transplant.
- Despite achieving complete response on PET-CT 3 months post consolidation, she progressed 9 months later with FDG avid disease.
- Relapse was complicated by haemophagoycytosis which responded initially to dexamethasone.
- She was ineligible for further intensive salvage chemotherapy due to poor performance status (3). She was commenced on ciclosporin, 100mg twice daily (dose later reduced due to renal impairment).
- The patient remained in ongoing remission until 19 months. Her renal function deteriorated with rising ferritin, consistent with relapse. She died 23 months later.

Fig 2: Lab Parameters following HLH Diagnosis

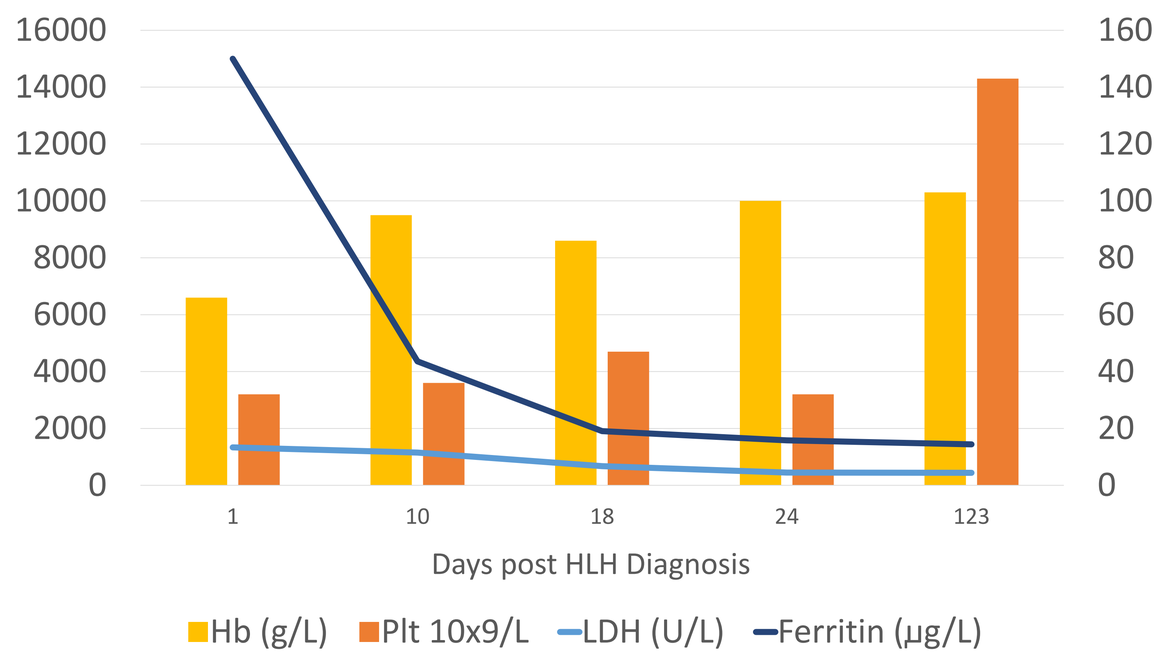


Fig 3: Summary

	CASE 1	CASE 2	CASE 3
Age at diagnosis	45	71	65
Performance status	1	2	1
Rationale for CSA/MMF	Bridge to allo SCT	Salvage	Salvage/palliative
Treatment prior to CSA/MMF	CHOP IVE/MTX Lenalidomide Cisplatin, Gemcitabine	CHOP, IT MTX	CHOP and IT MTX IVE Int dose MTX Autologous SCT
CR1	No: Deauville 3	No. Deauville 1.	Yes. Deauville 4
Time to 1st relapse	29months	5 weeks	12-13 weeks
Treatment post CSA	Allogeneic SCT (CSA bridge to allo)	MMF	NA
Non CSA complications	gVHD post allogeneic SCT	None	HLH
CSA toxicity	None	MAHA	None
Duration of response following initiation /MMF	Ongoing: 55 months	Ongoing: 26 months	Until 19 months Died: at 23 months

CONCLUSION

We described above favourable outcomes with ciclosporin and mycophenolate mofetil in relapsed/refractory AITL in variable settings; as a bridge to consolidation with transplant, post multiple lines of salvage therapy and as palliative treatment. Toxicity appears manageable. Other case reports suggest renal toxicity and EBV reactivation as most frequent complications. We suggest future trials incorporating oral immunosuppressive agents in this rare disease.

References: 1. Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. Blood. 2017 Mar 2;129(9):1095-1102. doi: 10.1182/blood-2016-09-692541. Epub 2017 Jan 23. PMID: 28115369.
2. Akihiro Ohmoto & Shigeo Fuji (2019) Cyclosporine for angioimmunoblastic T-cell lymphoma: a literature review, Expert Review of Hematology, 12:11, 975-981, DOI: 10.1080/17474086.2019.1652590

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