Autologous Stem Cell Transplantation in AL-Amyloidosis following Yttrium-90 Labelled Anti-CD66 Monoclonal Antibody as Sole Conditioning is Associated with Low Toxicity and Demonstrable Disease Responses

Kim H. Orchard MBBS PhD[1]*; Jon Langford MSc SRPharms[2]; Matthew Guy PhD[3]; Sofia Michopoulou PhD[3]; Gemma Lewis MPhys[3]; Julian Williams[4]; Clint Zvavamwe MSc[5]; Claire Hutchison BSc[1]; Jane Nunnick[6]; Amanda Blackwell SRN[1]; Pei-San Chan MSc[7]; Casper Wickham MSc[8]; Ann-Marie Quigley MD[9]; Mark Cook MBChB PhD[6]; Graham Jackson MD[10]; Philip Hawkins MD PhD[11], Ashu Wechalekar MD[11]

1. Wessex Blood and Marrow Transplant & Cell Therapy Program, Department of Haematology and BMT, University Hospital Southampton and Targeted Radiotherapy Group, University of Southampton UK
2. Targeted Radiotherapy Group, University of Southampton UK; 3. Department of Medical Physics, University Hospital Southampton; 4. Department of Nuclear Medicine, University Hospital Southampton; 5. Radiopharmacy, University Hospital Southampton 6. Centre for Clinical Haematology, Queen Elizabeth Hospital, Birmingham UK; 7. Radiopharmacy, Royal Free Hospital, London UK; 8. Department of Medical Physics, Royal Free Hospital, London UK; 9. Department of Nuclear Medicine, Royal Free Hospital, London UK
10. Department of Haematology, Freeman Hospital, Newcastle upon Tyne Hospitals, Newcastle UK; 11. National Amyloidosis Centre, University College London (Royal Free Campus), London UK

INTRODUCTION

Despite the introduction of new therapeutic agents autologous stem cell transplantation (ASCT) remains an important treatment option for patients with AL-amyloidosis (AL-A), resulting in improved organ function and survival in responding patients, however the utility is restricted due to the substantial toxicity of conventional ASCT conditioning in the vulnerable AL-A population. We report here the use of a monoclonal anti-CD66 monoclonal antibody (Besilesomab) radiolabelled with yttrium-90, TLX66 (^{90}Y-Besilesomab or ^{90}Y-anti-CD66) as the sole conditioning agent prior to ASCT in a phase I study in AL-A patients.

AIMS

This was a standard Phase I clinical trial with a '3 + 3' design, three patients at each of three levels of infused ^{90}Y-besilesomab activity as the only conditioning prior to ASCT.

Primary aim:

Tolerability of the targeted radiation in patients with AL-A undergoing ASCT.

Secondary aims:

1. Efficacy as determined by changes in tumour related free Light Chains (FLC)
2. Efficacy as determined by changed in Minimal Residual Disease (MRD) by FLOW cytometry
3. Cardiac recovery from changes in NT-proBNP levels
4. Time to disease progression and overall survival
5. Validate a dosimetry model in the context of AL-A
6. Engraftment of autologous stem cells
7. Production of Human anti-Murine antibodies (HAMA)

METHOD

The study had full ethical and regulatory approvals (EudraCT 2015-002231-18; ISRCTN 13400668).

Study Sponsor: University Hospital Southampton NHSFT

- 3 ascending infused radiation activity levels, 30, 40 and 45 MBq per kg body weight, each with 3 patients.
- Patients entered the study after fulfilling entry criteria and with informed consent.
- Prior to receiving ^{90}Y-besilesomab, organ dosimetry and biodistribution were determined using anti-CD66 labelled with indium-111 (^{111}In-anti-CD66) with sequential gamma camera imaging.
- Autologous stem cells were infused 14 days after ^{90}Y-anti-CD66 therapy
- Estimated absorbed radiation to critical organs was determined from an established dosimetry model, organ radiation dose expressed in Gray (Gy). Radiation dose limits of 45Gy for the bone marrow, 15Gy for the liver were used as safety measures.

RESULTS

Gamma camera images 24 hrs post infusion of ^{111}In-anti-CD66

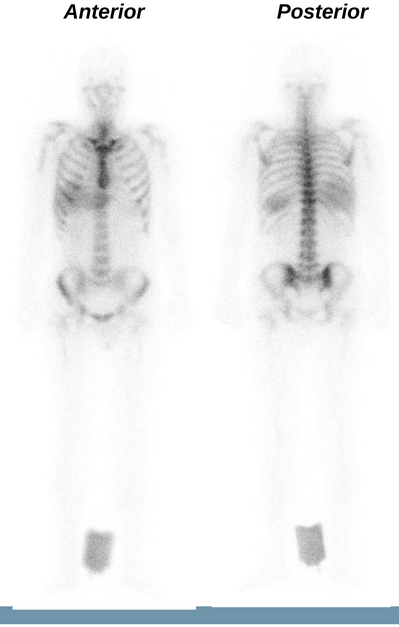

Table 1: Patient characteristics

Patient ID	Age Yrs	M/F	Underlying clone	Amyloid deposition	Previous number of treatments	Comorbidities	NYHA cardiac grade
Cohort 1							
CD6601-001	68	F	Lambda	Renal, spleen	4	Nephrotic syndrome CKD 1	3
CD6601-002	55	M	Kappa	Hepatic, renal, spleen	2	Nephrotic syndrome CKD 1	2
CD6601-003	69	M	lambda	Renal spleen cardiac	2	Nephrotic syndrome CKD 1 cardiac arrhythmias indwelling defibrillator	3
Cohort 2							
CD6602-004	56	M	Lambda	Renal	1	Nephrotic syndrome CKD 1	2
CD6603-005	58	M	Lambda	Gut	2	Previous GI haemorrhage	2
CD6601-007	67	M	Lambda	Cardiac tongue	3*	CKD 1	2
Cohort 3							
CD6601-008	70	F	Lambda	Renal	4*	Nephrotic syndrome CKD 3	1
CD6601-009	62	F	Lambda	Cardiac, renal	1	Nephrotic syndrome CKD 2	1
CD6601-010	69	M	Lambda	Cardiac, renal	3*	Nephrotic syndrome CKD 2	1

*Patients had received previous autologous SCT with HD melphalan; CKD – Chronic kidney disease, grades 1 - 4

Total number of AEs 47; Mild = 41; moderate = 3; severe = 3

Time to neutrophil engraftment: median = 13 days
Time to plt > 20 engraftment: median = 11 days
Time to plts >50 engraftment: median = 17 days

Responses: CR 2; PR 5; Stable disease 1; Progressive disease 1.

Of note two patients showed further, slow falls in clonal FLC beyond D+100 one achieving CR.

Table 2: Organ dosimetry and disease responses post ^{90}Y-anti-CD66 and ASCT.

		Estimated Organ Radiation Dose in Gray (Gy)						Disease response	Time to next treatment (months)
Patient ID	Infused activity MBq	BM	Liver	Spleen	Lung	Renal	Whole body	Response @ D+100	
Cohort 1									
CD66-01001	**1158**	**24.1**	6.3	38.6	1.4	13.6	0.7	CR	None
CD66-01002	**2262**	**41.1**	8.0	10.9	1.6	2.7	0.7	SD	24.0
CD66-01003	**2013**	**39.0**	3.9	31.4	1.3	3.4	0.8	PD	4.5
Cohort 2									
CD66-02004	**2985**	**44.5**	4.5	13.5	1.6	2.5	1.0	PR#	None
CD66-03005	**1867**	**45.0***	5.4	22.0	1.0	1.6	1.2	PR#	None
CD66-01007	**2323**	**31.2**	8.5	19.0	2.6	2.6	1.2	PR#	None
Cohort 3									
CD66-01008	**1734**	**31.6**	15.0	41.4	1.1	2.6	1.1	PR#	None
CD66-01009	**2019**	**37.6**	5.9	13.7	2.0	3.4	1.0	CR	None
CD66-01010	**2570**	**45.0***	9.2	53.1	1.9	2.2	1.1	PR	4.9

*Infused activity of ^{90}Y-anti-CD66 reduced to limit BM radiation dose to 45Gy #Clonal FLC continued to fall beyond D+100

Responses to the ^{90}Y-Besilesomab as demonstrated by a fall in measurable disease were seen in 6/8 patients. Two patients showed an increase in the percentage of malignant plasma cells post therapy.

Non-relapse mortality: ZERO

Overall survival: 100%

Time to next treatment: Only 3 patients required further treatment with a median follow-up of 11.13 months and a range of 4.5 – 24 m. Six (6) patients have not required further treatment.

CONCLUSIONS

This study achieved the primary and secondary end points.

TLX66 ^{90}Y-besilesomab was very well tolerated, no patients developed mucositis or therapy related diarrhoea and all maintained oral nutrition. No serious episodes of sepsis were reported and only two patients experienced a fever during the neutropenic phase, neither were serious.

Disease responses were seen in 7/9 patients with 2 CRs in the first 100 days post ASCT and a further CR post D100 resulting in 3CRs. Response durations were good for this heavily pre-treated group of patients.

The lack of toxicity and disease responses in previously heavily treated patients with AL-A would warrant further trials of the agent, potentially in patients who would not be fit for conventional ASCT with HD melphalan.

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TLX66 (^{90}Y-besilesomab) is wholly owned by Telix Pharmaceuticals.

CONTACT INFORMATION

kho@soton.ac.uk