The Effect of Bevacizumab on Vestibular Schwannoma Related to Neurofibromatosis Type 2

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Abstract

Introduction: We describe an Australian experience of infusional bevacizumab for vestibular schwannoma (VS) in neurofibromatosis type 2 patients, with specific focus on 3-dimensional tumour volume and audiometry.

Method: Data was pooled from patients with symptomatic or progressive VS from 2009 to April 2018. Tumours were assessed as total volume per patient. Bevacizumab infusions were administered every 2-4 weeks. 3-D volumetric response (cm^3) was determined through serial magnetic resonance imaging, at baseline and at 3-6-month intervals, until cessation of infusions following progression or prior to surgery. Volumetric response was defined as a reduction of volume ³ 20%, from baseline. Patients underwent interval pure tone audiometry. A decrease in the average pure tone analyses by 10dB indicated response.

Results: Twenty-one VS tumours were identified in eleven patients. Median age was 26 (range 13 – 67yr). Average baseline tumour volume was 14.17cm^3 (range 1.45cm^3 - 38.51cm^3). Tumour volume reduction >20% was shown in 7/11 patients (64%), indicating partial response, 2/11 (18%) patients showed stable disease, and 2/11 (18%) progressed. Average percentage tumour volume change was +4.45% from baseline (range -57% to 241%). 16 individual ears were tested, 3/16 (19%) of ears showed an average decibel reduction of 10dB or more, indicating response (average change 2.5dB, range -36dB to 81dB). 10/16 (63%) showed stable hearing, and 3/16 (19%) showed hearing deterioration.

Conclusion: Bevacizumab is a useful agent for reducing tumour volume and improving hearing losses due to vestibular schwannoma in neurofibromatosis type 2 patients. These results reflect results described from the United Kingdom and United States.

Key Words:

Bevacizumab, Vestibular Schwannoma, Neurofibromatosis Type 2, 3-D Volumetric Analysis, Audiometry

Introduction

Neurofibromatosis type 2 (NF2) is a rare, predominantly hereditary, genetic mutation of the NF2 suppressor gene on chromosome 22. It occurs as an autosomal dominant inherited mutation, or as a sporadic somatic mutation, with up to 50% of patients presenting with a de novo mutation (Evans, 2009; Evans et al., 2019). Individuals with NF2 are at high risk of developing tumours of the central nervous system; typically vestibular schwannomas (VS) of the eighth cranial nerve, but also meningiomas, ependymomas and gliomas (Evans, Sainio, & Baser, 2000)

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The mean age of onset of symptomatic VS is 20-30 years (Parry et al., 1994). Patients who develop VS tumours in childhood are expected to live into their thirties, and this is improving with modern advancements (Evans et al., 2019). Larger tumours incur worse prognosis (Otsuka, Saito, Nagatani, & Yoshida, 2003). Diagnosis typically follows investigation of hearing loss or visual disturbance. VS tumours are usually bilateral, and associated with sensorineural hearing dysfunction, headaches, and, on occasion, cranial nerve neuropathy (Bell's palsy or trigeminal disturbance), all of which can have significant impact on quality of life. Plotkin and colleagues suggests an average linear growth rate of 1.9mm/year (Plotkin et al., 2012; Slattery, Fisher, Iqbal, & Oppenhiemer, 2004).

Hearing loss is usually progressive, and has been traditionally managed with either surgical resection or radiation of the VS tumour (Halliday, Parry, & Evans, 2019; Kazim, Shamim, Enam, & Bari, 2011; Phi et al., 2009; Van Gompel et al., 2018). If left unattended, VS can cause increased intracranial pressure and even death (Evans et al., 2000). While the techniques on surgical resection and radiotherapy have been refined over many years, these modalities often leave patients with permanent deafness. There is a rare potential for benign tumours to undergo malignant transformation, thought to be related to previous irradiation (Evans, Birch, Ramsden, Sharif, & Baser, 2006). Therefore, while patients can achieve an extended prognosis, it is often at the expense of their quality of life (Otsuka et al., 2003).

There have been multiple studies investigating systemic options for NF2 related VS. Systemic treatment is complicated by the elusiveness of the blood-brain barrier, and multiple monoclonal antibody and small molecule inhibitor agents have been proposed (Evans et al., 2009; Goutagny & Kalamarides, 2018; Karajannis et al., 2012; Nigro et al., 2019).

Bevacizumab in Neurofibromatosis Type 2

VS tumours express vasculo-endothelial growth factor (VEGF) on immunohistochemical profiling (Li et al., 2016; Mautner et al., 2010; Plotkin, Stemmer-Rachamimov, et al., 2009). Several studies have investigated the effect bevacizumab, an antiangiogenic agent specifically targeting VEGF, to reduce the volume and associated hearing impairment related to VS tumours (Alanin et al., 2015; Hochart et al., 2015; Huang et al., 2018; Mautner et al., 2010; Morris et al., 2016; Nigro et al., 2019; Plotkin, Stemmer-Rachamimov, et al., 2009). In a cohort of ten patients with ten index tumours, nine tumours showed treatment effect, and four patients maintained response during 11-16 month follow up (Plotkin, Stemmer-Rachamimov, et al., 2009). Overall, a median volume reduction of 26% was observed. Of the seven patients who were eligible for audiometric analysis, four showed response, two had stable hearing and one deteriorated. This was followed up with a larger retrospective study looking at thirty-one patients, including the ten originals (Plotkin et al., 2012). Again, volumetric and hearing outcomes were favourable; seventeen of thirty-one lesions had a positive volume response, and seventeen of twenty-three showed a positive audiometric response. Results were durable beyond one year, and more than 50% of patients had maintained their response beyond three years. Toxicity was typically manageable. Alanin (2015) and colleagues conducted a 12 patient study and showed partial volumetric response in 50% of patients, and 11% response in hearing.

Morris (2016) and colleagues co-ordinated a similar study for NF2 VS patients based in the UK. Data from sixty-one patients receiving bevacizumab illustrated a partial response of tumour growth occurring in 39% of all tumours, and stable disease in 51%. 86% of patients had either a stabilisation or improvement of their hearing.

In Australia, bevacizumab is not currently funded by the Pharmaceutical Benefits Scheme for this indication, and patients are currently self- funding infusions. Access programmes established throughout public hospitals can assist with costs in the short term, however are unsustainable for ongoing infusions.

Audiometric Assessment

Plotkin and colleagues have provided recommendations for audiometric assessment in NF2 VS (Plotkin, Blakeley, et al., 2013; Plotkin, Halpin, et al., 2009). Pure Tone Audiometry (PTA) has a sensitivity of 92% and a

specificity of 94% in detecting sensorineural hearing impairment. Audiometric volumes are tested from 15-30 decibels (25-30 dB for adults, 15-20 dB for children), and aims to challenge patients with tones ranging from 500 to 4000Hz, which is reflective of the normal speech spectrum (Plotkin, Blakeley, et al., 2013; Plotkin, Halpin, et al., 2009). Word Recognition Score (WRS) assessment is the most accurate reflection of the speech spectrum, and is more widely utilised in NF2 (Dombi et al., 2013; Plotkin, Ardern-Holmes, et al., 2013)

Methods

This paper is a retrospective analysis describing the effect of bevacizumab on tumour volume and audiometry in VS in NF2 patients in Australia. The primary endpoint is change in tumour volume and the secondary endpoint is change in audiometry.

Study design and ethics

This analysis pools data from two periods of treatment, looking at a total of eleven NF2 patients. Seven patients were followed from 2009 through to 2013, and four patients were followed from 2013, through to April 2018. This study was approved by the local Human Research Ethics Committee (10CHW14). Patients were informed of the utilisation of their radiological and audiometric information for the purposes of this study. Patient information was de-identified and kept under password protected security. There was no interference with standard treatment procedures and no additional interactions with patients.

Patients

All patients met clinical criteria for NF2. Patients were identified over two time periods. Patients from 2009 to 2013 were evaluated at Westmead Children's Hospital or Westmead Hospital. Patients were included from three sites in New South Wales (Prince of Wales Hospital, Liverpool Hospital and Royal Prince Alfred Hospital), Perth (Hollywood Private Hospital, Western Australia), Adelaide (Flinders Medical Centre, South Australia), and the Gold Coast (Gold Coast Cancer Centre and Day Hospital, Queensland). Patients from 2013 to 2018 were included from Westmead Hospital (New South Wales).

Patients were retrospectively analysed from the beginning of their treatment until February 2013 for the earlier cohort, and until April 2018 for the later. Patient information including age, gender and clinical response to treatment, was collected through the hospital -centered electronic databases- (PowerChart and ARIA) and paper records. MRIs were accessed through Inteleviewer, an electronic image viewing portal with secure access. Audiometry assessments were conducted through local audiometry services.

Assessment

Patients were screened for factors that would increase risk of bevacizumab side effects; including uncontrolled hypertension, prior stroke, vascular disease (both cardiac and peripheral vascular), previous or current deep vein thrombosis, personal or family history of coagulation disorders, hepatic dysfunction or renal dysfunction, or haematologic dysfunction (MacKeith et al., 2018; Morris et al., 2016). No patients were pregnant or breast-feeding during treatment. Advice was provided to patients of reproductive age to use contraception and avoid pregnancy during treatment. Fertility preservation was discussed with patients prior to commencing therapy. Patients were clinically reviewed in between bevacizumab cycles. Blood pressure and urinalysis was taken prior to every infusion. A quality of life questionnaire was incorporated into the earlier cohort assessment, however this was not conducted in the later cohort and as such has not been included in this analysis.

Bevacizumab infusions

Patients received bevacizumab infusions through the chemotherapy suites at Westmead Hospital, Westmead Children's Hospital, Prince of Wales Hospital, Liverpool Hospital, Royal Prince Alfred Hospital, Hollywood Private Hospital, Flinders Medical Centre and the Gold Coast Cancer Centre and Day Hospital. Bevacizumab infusions were financed via a combination of self-funding, pharmaceutical special access schemes and compassionate access through the Hospital Drug Committee.

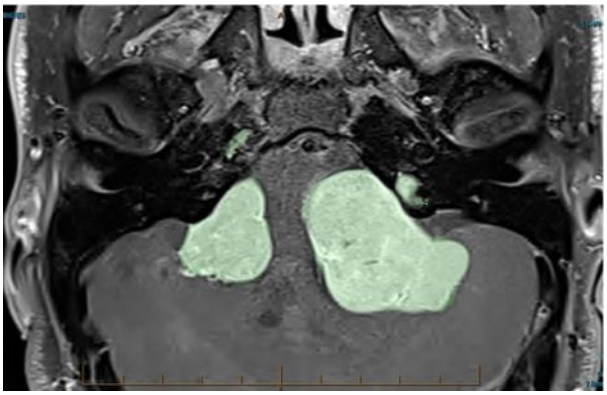
Dose adjustments were made based on clinically assessed adverse effects, such as hypertension, proteinuria, bleeding, clotting and general tolerability (Farschtschi, Kollmann, Dalchow, Stein, & Mautner, 2015; Morris et al., 2017; Slusarz, Merker, Muzikansky, Francis, & Plotkin, 2014). Infusions were withheld prior to any surgical procedures to allow for drug washout, and minimisation of bleeding and clotting risks, and delays in wound healing.

Radiological measurement of response

Magnetic Resonance Imaging (MRI) is the current gold standard for NF2 VS imaging (Dombi et al., 2013; MacKeith et al., 2018; Plotkin, Blakeley, et al., 2013). MRI brain series were collected at baseline and 3 month intervals throughout treatment duration. Various imaging facilities were utilised, based on patient preference and convenience. Attempts wherever possible to complete imaging at the same imaging centre was encouraged, for continuity of imaging quality. Three-dimensional (3-D) volumetric assessment is more sensitive and specific than two-dimensional (2-D) analysis and can detect changing volumes earlier than 2-D measurements. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria are most reliable and have been accepted widely as the standard criteria for NF2 related lesions (Dombi et al., 2013; Plotkin, Halpin, et al., 2009). Significant clinical response is based upon a 20% change in 3-D volumetric analysis; a 20% decrease indicating partial response, a 20% increase indicating progression, and any measures within these parameters considered stable disease. Under this criterion, surgery for the target lesion also constitutes radiological progression.

For the earlier cohort, 3-D volumetric analysis was sought from an external company, NFtumormetrics Group, Medical Imaging Centre, Massachusetts General Hospital, Boston; and two local radiologists at Westmead Hospital. For the later cohort, volumetric measurements were recorded from two separate investigators; a medical oncology advanced trainee, and a radiology fellow. Measurements were taken under guidance from a senior radiologist and medical oncologist at Westmead Hospital. T1 gadolinium contrast images were analysed, with sliced series ranging 1mm-5mm in the axial plane. VS measurements were collected independently, and then collated for statistical analysis. 3-D Volumetric Analysis of tumour size was obtained using electronic Inteleviewer software (version 4-12-1-P115) Figure 1. Scans conducted at alternative MRI sites could be imported to Inteleviewer, for standardised analysis. VS tumours were identified as target lesions, and other lesions (non-vestibular schwannoma, meningioma, optic nerve sheath tumours) were identified and measured where appropriate, though not included in our final analysis. Data from both time periods was combined an analysed as a single dataset.

Figure 1: Volumetric Measure of Bilateral VS



Audiometric measurement of response

Patients underwent audiometric assessment, at baseline and then 3-6-month intervals. Various audiometric labs were used, based on patient preference and convenience. A combination of PTA and WRS results were collected. All patients underwent PTA testing, however, WRS testing was not routinely conducted, and thus was not included in the final analysis. PTA results were measured and analysed individually for each ear. A decrease in the average PTA by 10dB indicated response (Plotkin, Halpin, et al., 2009).

Statistical analysis

Statistical analysis was guided by a statistician. Simple descriptive statistics were calculated using Microsoft Excel Workbook, v16.25. NFtumormetrics volumes and local volumes were pooled and averaged for each patient for each scan. Absolute change in volume was expressed as a percentage for each patient.

Volume change percentage was measured from baseline through until last MRI on treatment. Serial PTA results were also calculated in the same manner. PTA readings were averaged across frequencies from 250Hz-8000Hz and expressed in decibels (dB).

Results

Twenty-one VS tumours were identified in eleven patients across both time periods. All patients had either clinical or radiological progression of VS tumours on commencement of bevacizumab infusions. The median patient age was 26 (range 13-67 years). Results are summarised in Table 1 below.

Seven patients were identified from 2009-2013, three females and four males. One patient only had a unilateral VS tumour. Five patients only had unilateral hearing intact at the time of commencement of infusions. Three patients also experienced symptoms of brainstem compression. One patient had significant NF2 related disability, with unilateral deafness and bilateral blindness. Four patients had other intracranial lesions, including meningiomas, trigeminal schwannoma and optic nerve sheath tumours.

One patient received prior small molecule therapy (imatinib) before commencing bevacizumab. Imatinib was ineffective in this patient and was ceased five months prior to the commencement of bevacizumab therapy. Patients with co-morbid meningiomas, who were included within the first time period were concurrently prescribed a somatostatin analogue, in light of data indicating potential benefit for meningiomas (Chamberlain, Glantz, & Fadul, 2007).

Four patients were analysed from 2013 to 2018, one female and three males. All patients had bilateral VS tumours. One patient developed brainstem compression prior to commencement of bevacizumab. One patient with hearing loss was also experiencing

Table 1: Results Summary for Tumour Volume and Audiometry Response

Patient	Age (years)	Unilateral or Bilateral Tumour	Duration of Treatment (months)	Baseline Total Tumour Volume (cm3)	Best Volume Response % (response)	Best Hearing Response (right/ left ear)
1	22	U	27	10.79	-53 (PR	R: PR, L: not tested
2	23	B	24	5.55	-21 (PR)	R: SD**, L: PD**
3	33	B	12	16.26	-32 (PR)	R: PD, L: PD
4	22	B	9	18.51	-37 (PR)	R: PR, L: SD
5	31	B	9	38.51	-28 (PR)	R: not tested, L: NA*
6	33	B	15	3.76	-25 (PR)	R: SD, L: SD
7	13	B	9	1.77	+17 (SD)	R: SD, L: not tested
8	15	B	47	1.45	+241 (PD)	R: NA*, L: NA *
9	14	B	9	13.38	+14 (SD)	R: SD, L: SD
10	67	B	9	4.25	-57 (PR)	R: SD, L: SD
11	17	B	18	37.9	+30 (PD)	R: SD then PD, L: PR then PD
Mean:	26		17	14.17	+4.45	+2.5 (decibels)

PR: partial response, SD: stable disease, PD: progressive disease
* Patients had single data available, not included in analysis
** Patient did not have baseline data, however serial data available for analysis
not tested: no data collected (baseline deafness)

neuralgia from trigeminal V3 trigeminal nerve compression of the VS tumour. One patient had a large tumour causing compression of the optic nerve and visual impairment of the right eye. This patient had complete vision loss in the left eye secondary to a prior left VS tumour.

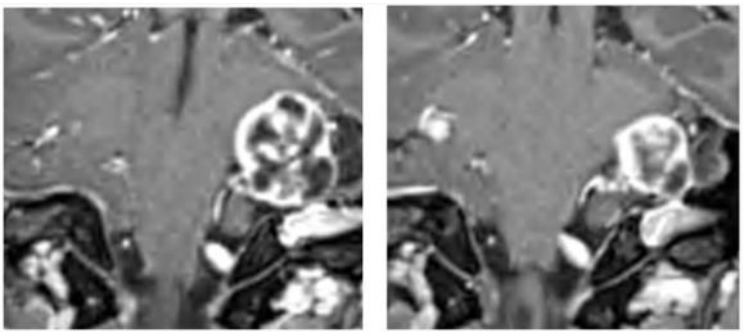
One patient had transferred from the children's oncology service to the adult oncology service. They had been treated previously with bevacizumab in the Children's Hospital and had ceased therapy for surgical resection. This patient was restarted on bevacizumab after a treatment break following surgery.

Most patients were commenced on a dose of 5mg/kg given every fortnight. One patient (treated with concurrent imatinib) was commenced on 15mg/kg every 3 weeks, which was subsequently reduced following disease stabilisation, to 7.5mg/kg given every 3 weeks. There was variability in the frequency of cycles, ranging from two to four weeks. Median duration of therapy was 9 months (range 9-47 months), with an average of 17 months.

Tumour Volume Response

The average baseline total tumour volume per patient was 14.17cm^3 (range 1.45cm^3 - 38.51cm^3). Reduction in tumour volume of >20%, indicating a partial response was identified in seven out of eleven patients (64%) (Figure 2) (Dombi et al., 2013). The average volume change was an increase by 4.45%, ranging from a reduction of 57%, through to an increase of 241% from baseline measurement, however this patient had the smallest baseline volume. Of the four patients who did not achieve a partial response, two had stable disease (18%) and two had progression (18%) of disease.

Figure 2: Volume Change in Unilateral VS



At 12 months, six patients were still receiving infusions. The longest treatment period was 47 months. The average length of treatment was 17 months. Reasons for stopping were progression of disease, progression to surgical resection or cessation of funding for infusions.

Pure Tone Audiometry Analysis

Results were available for 16 ears. Two patients only had a single ear tested from baseline. Two patients had a single result for each ear available, and as such were unable to be analysed for decibel change. One patient did not have a baseline data set available, however had serial PTA results available and as such was included in the analysis. Follow up for PTA analysis ranged from 6- 30 months, with a median of 15 months.

Of the sixteen ears tested, three responded, 19%. 10/16 ears maintained a decibel change between -10dB to 10dB. Three ears showed progression of hearing impairment. The average decibel change was 2.5dB, (range -36 to 81dB).

Toxicities

One patient was hospitalised with a viral illness and haematemesis, who also developed thrombosis around in intravenous catheter. Bevacizumab was temporarily withheld, cautiously restarted after anticoagulation, with no recurrence of either bleeding or clotting events. No patients were documented to have suffered from stroke during their bevacizumab treatment period.

The main toxicities documented were hypertension, proteinuria and fatigue, all grade 1-2 (National Cancer, 2010). Two patients developed both hypertension and proteinuria. Management for these toxicities included antihypertensives for management of blood

pressure, along with a dose and frequency reduction in the bevacizumab dosage for effected patients. No patients ceased therapy due to toxicity. Fatigue was an intermittent symptom for most patients and likely multifactorial.

On informal follow up, at least six patients ceased bevacizumab infusions due to cessation of compassionate funding, where self-funding was not a feasible option. One patient stopped infusions to proceed with surgery, another stopped to proceed with radiation. At least two patients continued to self-fund infusions.

Discussion

This study demonstrates a beneficial effect of bevacizumab in control of VS and hearing in patients with NF2. We believe this study represents the first published experience amongst Australian NF2 patients treated with bevacizumab and our results are reflective of those in international centres.

Plotkin (2009) showed evidence of radiological response in 6/10 (60%) of patients. Similarly, Alanin (2015) studied a cohort of 12 patients and found 6/12 (50%) of patients had a partial response.

Plotkin (2012) again collaborated and studied thirty-one patients who showed 53% of patients responding in a larger cohort of thirty-one patients, with fifty-one measurable lesions. Morris (2016) conducted the largest trial, looking at sixty-one patients, and found 39% of their cohort showed evidence of response.

Alanin (2015) reported a similar hearing stabilisation effect of bevacizumab in a total of 9 ears across their 12-patient cohort, and describe a response in 11%, stable hearing in 79% and deterioration of hearing in 22%. We recognise that WRS analysis is a more sensitive measure of hearing in NF2 patients, however, the paucity of available WRS results within our patient cohort prevented statistical analysis.

Bevacizumab toxicities were within the expected spectrum and manageable, with appropriate dose and frequency modifications (Morris et al., 2017). There was only one major grade 4 toxicity, and no treatment related deaths.

Limitations

The heterogeneity of volumetric assessment may have minor impact upon the accuracy of our results. Although both time periods cohort measurements were standardised within each separate time period, it would have been preferential to have a standardised assessment process across both time periods. Dombi (2013) and colleagues do not specify whether manual measurement is preferential over automated measurement, but simply comment that measurements should be consistent across the cohort and analysed centrally which we upheld within the confines of our study. Financial restraints posed a barrier to accessing off site automated analysis in the second cohort. While measurements were simple to obtain on manual measurement, manual techniques were time consuming and would prove inefficient in larger cohorts outside of a study environment.

Future direction

Given the durability and reproducibility of response rates, bevacizumab should be considered as part of the frontline management of VS tumours. It would offer a less invasive and generally more tolerable side effect profile to surgery or radiotherapy, without the risk of malignant transformation (Evans et al., 2006).

Bevacizumab may reduce the use of steroids to manage VS symptoms, which in turn would reduce steroid related morbidity in patients who survive for extended periods with VS tumours and are often prescribed protracted courses of steroids and incur many steroid related co-morbidities.

Li (2016) and colleagues have been investigating the use of biochemical characteristics and changes in serial ‘dynamic contrast enhanced’ scans to help identify a subgroup within VS tumours who are more likely to respond to VEGF inhibition with bevacizumab. This may help to further triage and streamline treatment modalities to offer the

most clinically and financially effective treatment option to NF2 patients.

Ideally, bevacizumab would be incorporated into the national funded registry (in Australia, the Pharmaceutical Benefits Scheme) of available treatment options for NF2 patients, thus alleviating the financial burden placed upon patients and their families in an attempt to access treatment.

Conclusion

Bevacizumab has been shown to be effective drug in helping to reduce tumour volume and improve hearing. The Australian experience is comparable to that illustrated in both the US and the UK, using standardised volumetric measurement techniques and response criteria, and acceptable appropriation of audiometric results.

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Australasian Neuroscience Nurses Day May 4th

On 4 May, 1974, Tonnie Koenen organised the first meeting of Australasian neuroscience nurses in Canberra, during the Neurosurgical Society of Australasia's annual meeting.

About 30 nurses met to formally establish the Australasian Neurosurgical Nurses' Association. Since that time, Neuroscience nurses have continued to promote collaboration with other nurses and other health professionals in a committed effort to the professional development and education of nurses within the specialty of neuroscience. We celebrate this and the beginning of our Association on our Australasian Neuroscience Nurses Day, every 4th of May.

The Covid-19 pandemic has shown the world the important role that nurses play within our healthcare systems.

During this past year we have been exposed to enormous pressures and challenges. Australasian Neuroscience Nurses day is a day to reset and take the opportunity to reflect.

We give thanks this year for the advancements that have led to improvements in the health of so many.

We work to support new breakthroughs in overcoming neurological diseases and disorders.

We hope for this pandemic to end and for no more lives to be lost.

We support our colleagues as we all work to provide the best care that we can, always embracing change and innovation.

We hope that we can have the wisdom, knowledge and vision to work together and support each other during the often long and lonely hours.

Linda