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FINAL REPORT

Project / Program Title		Optimizing detection of pulmonary complications in children following bone marrow transplantation: a prospective longitudinal study
Name		Clinical A/Prof Paul Robinson
Award Received		2016 Robert Maple-Brown Research Establishment Fellowship
Report Date		25 August 2019
Chief Investigator / Supervisor		Clinical A/Prof Paul Robinson
Administering Institution		The Sydney Children's Hospitals Network
Funding Period	Start Date:	1 January 2016
	Finish Date:	1 June 2019

PROJECT SUMMARY

Post-bone marrow transplantation (BMT), chronic Graft Versus Host Disease (cGVHD) is a significant cause of morbidity and mortality and can affect many organ systems including the lungs. Lung involvement is characterised by progressive obstruction of peripheral airways resulting in loss of lung function and eventual death. The drop in lung function that occurs as a result of this process is currently detected using a technique called spirometry, and called “Bronchiolitis Obliterans Syndrome“(BOS). However spirometry is insensitive to changes occurring in the lung periphery and as a result disease is advanced by the time BOS is detected and prognosis is poor at that stage. Novel peripheral lung function tests such as Multiple Breath Washout (MBW) and Forced Oscillation Technique (FOT) offer better insight into peripheral airway function, and also offer better feasibility in younger populations. The utility of these tests in the post- BMT setting remains unclear. This study sought to explore that utility by assessed children pre-BMT (“at baseline”) and at regular intervals for the first 3 years post-BMT, using spirometry, MBW and FOT. Twenty four children were recruited to participate in the study.

The main findings of the study were as follows:

- Feasibility was higher for MBW and FOT, compared to spirometry: 88% and 83%, vs. 79%, across study visits, respectively. Subjects aged 6 years or less found it much tougher to perform spirometry than MBW or FOT.
- In subjects that developed BOS (n=3), at the time of BOS diagnosis, the magnitude of change in peripheral airway function, detected using MBW and FOT, compared to the pre-BMT levels, was several magnitudes greater than changes observed in spirometry
- MBW provided an earlier signal of impairment in both of the children where an earlier lung function assessment had been performed after BMT: in these 2 subjects MBW became abnormal 26 and 207 days prior to the spirometry-based BOS diagnosis. In the third subject

he was physically unable to perform lung function testing until day 105, by which time his spirometry was consistent with BOS and all his lung function testing showed marked abnormality.

- In subjects that satisfied criteria for being “at risk” of BOS (termed “BOS 0p”, n=8), MBW parameters were significantly raised (or abnormal) compared to those that had remained unaffected (n=9) at the end of the 3 year monitoring period.
- Overall, during the 3 year follow up, MBW became abnormal earlier than spirometry: it took 286 days for 50% of the cohort to develop abnormality in their MBW, compared to taking 471 days for 50% of our cohort becoming abnormal in their spirometry

The abnormality that developed in MBW parameters suggests increasing peripheral airway obstruction in these children with BOS or at risk of developing BOS. FOT was also markedly abnormal in Overall, this suggests that MBW and FOT have clinical utility in the monitoring of lung function in children post-BMT. MBW appears to provide early insight into later BOS diagnosis. Future studies will investigate whether these tools could allow clinicians to treat lung involvement sooner and prevent significant morbidity.

PROJECT AIMS / OBJECTIVES

The aims of this study were as follows:

1. To prospectively follow subjects post-BMT and to describe the pattern of lung function abnormality observed in MBW and FOT in BOS, BOS 0p and No BOS subjects.
2. To investigate whether MBW and FOT abnormality preceded the abnormality observed in spirometry

Recruitment and 36 months of prospective follow-up has been completed. Data analysis has been completed.

A manuscript for this study is currently being prepared. We anticipate submission by the end of 2019.

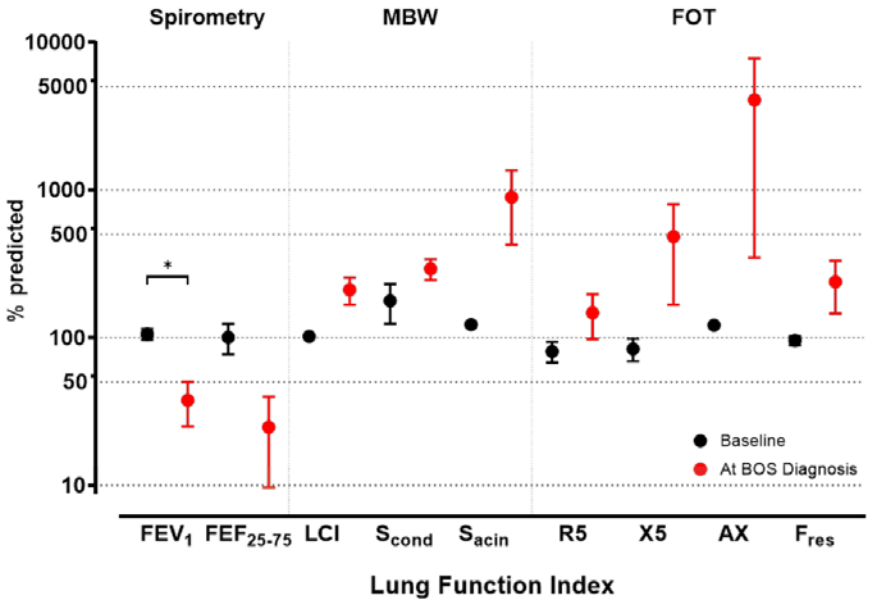
SIGNIFICANCE AND OUTCOMES

Outcomes (or Results) from the study:

24 subjects were recruited from March 2014 to April 2016. Overall, each subject attended and contributed data for an average (SD) of 12.4 (4.6) visits over 36 months of follow-up. Feasibility of spirometry, MBW and FOT was between 79-88% of all visits. Definite BOS and BOS 0p was detected in 3/24 (12.5%) and 8/24 (33.3%) respectively.

Abnormality in MBW appeared prior to BOS diagnosis in 2 out of 3 subjects. The third subject was unfortunately unable to perform lung function testing prior to 4 months post-BMT due to severe acute skin GVHD and was diagnosed with BOS at the first feasible follow up time point (4 months post BMT). He had abnormal in spirometry, MBW and FOT at the first opportunity to perform lung function testing. In those that developed BOS, a repeatable pattern of pronounced abnormality in peripheral airway function indices (MBW and FOT) was seen. The figure below compares the change in all indices, compared to baseline (i.e. pre BMT) at the date of formal BOS diagnosis. The observed changes in MBW and FOT were several magnitudes greater than changes seen in spirometry (see Figure 1, note the log10 scale used for the y-axis).

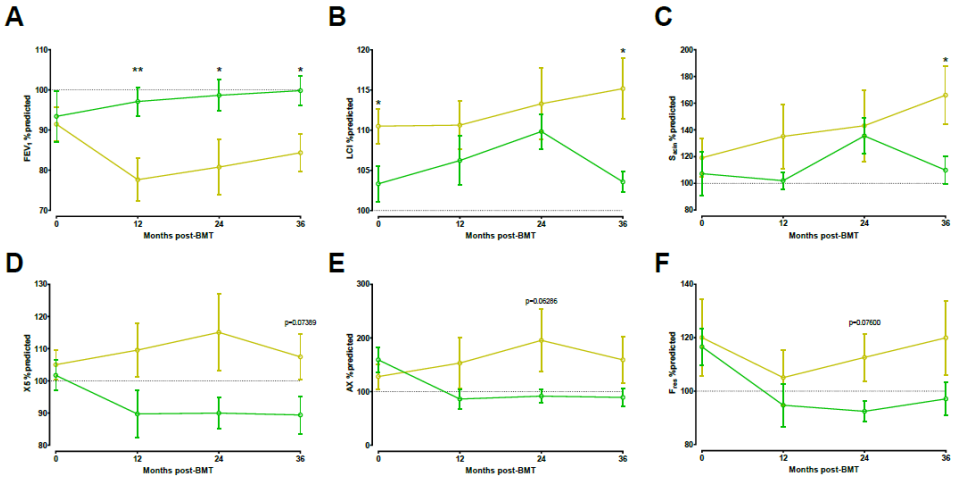
Figure 1. Greater change in FOT and MBW indices, compared to spirometry, at the time of formal BOS diagnosis (red symbols), compared to pre-BMT value (black symbol).



With greater severity of BOS, a steeper rate of lung function deterioration was seen in all three lung function tests used (data not shown).

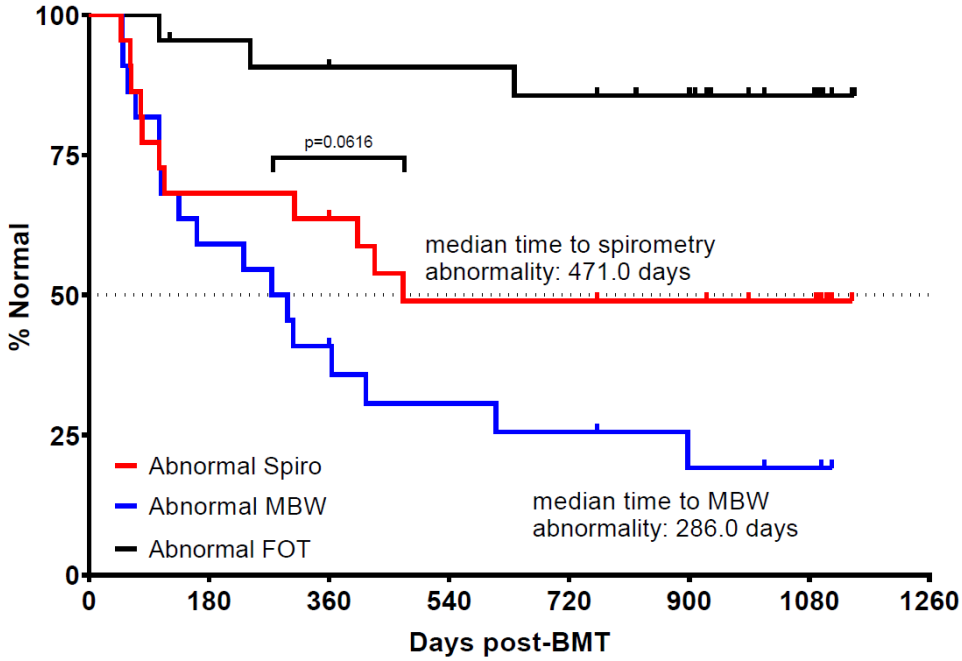
We then examined if there was a difference in peripheral airway function in those children who met the criteria for BOS 0p (the at risk category for later BOS), compared to those who maintained spirometry within 10% of the baseline level (i.e. No BOS). BOS 0p subjects had significantly higher MBW (LCI, Sacin) and FOT (X5, AX, Fres) parameters (see Figure 2 below), compared to No BOS subjects. Taken together, these results indicate that peripheral airway obstruction and increasing lung “stiffness” were a feature of children with BOS 0p, when compared to No BOS subjects.

Figure 2. Change in MBW (panels B-C) and FOT (panels D-F) over the 36 month follow up period, compared to FEV1 (Panel A), in subjects with BOS 0p and those who remained No BOS.



Across the entire cohort, we also examined whether MBW and FOT parameters became abnormal at an earlier time point compared to the conventional monitoring tool spirometry. The median time to abnormality for MBW occurred much earlier at 286 days post-BMT, compared to 471 days post-BMT for spirometry (see Figure 3 below), an almost 200 day difference. This difference trended towards statistical significance (p=0.06).

Figure 3. Time to abnormality plot for MBW, FOT and spirometry across the entire cohort.



Significance

Taken together, the results of this study show that (1) BOS has a characteristic and repeatable pattern of significant peripheral airway function abnormality (based on MBW and FOT changes), (2) that the changes in MBW occur at an earlier time point that the current monitoring tool spirometry in BOS subjects, and (3) that those at increased risk of BOS also have detectable abnormalities in peripheral airway function. This demonstrated that MBW may be useful in the early detection of BOS in the paediatric post-BMT setting. This important pilot data will be used for future grant applications to fund larger multi-centre studies investigating the utility of intervention based on the MBW change post BMT.

PUBLICATIONS / PRESENTATIONS

Abstracts were presented as posters/oral presentations at 3 international conferences over the last 3 months:

- Transplantation and Cellular Therapy Meetings 2019 in Houston, TX USA
- Thoracic Society of Australia and New Zealand 2019 Annual Scientific Meeting on the Gold Coast, QLD
- American Thoracic Society 2019 Annual Meeting in Dallas, TX, USA

We are planning to submit a formal manuscript of the study findings to a leading respiratory medicine journal by the 4th quarter of 2019.

ACKNOWLEDGEMENTS

The RACP Foundation was acknowledged for each abstract and poster that was published.

We will acknowledge the RACP Foundation's gracious help when the study is published.