RACP
Specialists. Together
EDUCATE ADVOCATE INNOVATE

RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Follicular lymphoma: novel approaches to improving the diagnostic and treatment paradigm
Name		Dr Allison Barraclough
Award Received		2020 RACP Fellows Research Entry Scholarship
Report Date		01/03/2021
Funding Period	Start Date:	01/07/2019
	Finish Date:	31/01/2021

PROJECT SUMMARY

Follicular lymphoma (FL) is the most common indolent lymphoma, constituting 20-30% of all non-Hodgkin lymphoma (NHL). Although FL is considered to be slowly progressive and incurable in most cases, it is a heterogenous disease. Grading is one of the ways to delineate the aggressiveness of FL. This is based on the relative number of small cells to large cells. Grade (G) 1-3A FL typically is an indolent disease with a course spanning decades, whereas G3B FL is considered to be clinically aggressive. While conventional treatment for G3B is urgent chemotherapy, asymptomatic

G1-3A can potentially be observed. Thus accurate grading of FL has major treatment implications. Unfortunately, histological grading is subjective and disagreement exists between experts in up to 40% of cases. Using cutting edge molecular technology, we are determining if each FL grade has its own unique genetic signature thus creating an objective classification system.

Despite remarkable progress in long-term disease control, a subset of FL patients (~15-20%) experience dismal outcomes with 5-year overall survival of 38%. Improved strategies are essential to identify this poor risk group. Positron emission tomography/Computed tomography (PET/CT) has become standard imaging for staging lymphoma and is widely available. I am assessing if aspects of PET/CT, such as the intensity and volume of the lymphoma at diagnosis can identify these patients who respond poorly to treatment.

Although overall survival (OS) for FL now exceeds 12 years; most patients will require multiple lines of treatment in their life time. Standard treatment with chemotherapy is profoundly immunosupressive and can result in severe life threatening infections and other significant side-effects. While adequate disease control can be achieved with these measures, the toxicity is a major concern, particularly for elderly patients. Effective, low toxicity treatment strategies are needed. The ‘First-line treatment for FL using Nivolumab plus Rituximab’ (1st FLOR) is a phase II investigator-initiated trial, conducted by my research group, utilising a chemotherapy-free approach designed to manipulate the patients’ own immune system to eradicate disease and limit toxicity.

I have evaluated the safety and feasibility of this combination, and have demonstrated, on interim analysis that this combination has a favourable toxicity profile and excellent overall and complete response rates potentially providing patients an alternative to traditional chemotherapy. The final analysis is underway.

PROJECT AIMS / OBJECTIVES

Aims:
1. Compare clinical characteristics & outcomes in the largest planned cohort of high grade FL, with low grade FL and Diffuse Large B-cell lymphoma.
- Collaborators: both nationally and internationally have contributed data.
- Interim analysis completed and decision made to expand cohort to include G3A patients.
- Data received and statistical analysis is underway.
- Manuscript submission is planned for May 2021.
2. Undertake genetic analysis on tissue from G1-3BFL diagnostic tissue samples
- Initial exploratory analysis using RNA sequencing to determine patterns of gene expression performed on 5 formalin fixed paraffin embedded tissue samples from each FL grade.
- These initial findings have grouped the FL grades into distinct subtypes.
- RNA sequencing performed on larger validation cohort. Analyses of sequencing data underway.
- Plan for abstract submission May 2021 to the International Conference on Malignant Lymphoma
3. Assess the prognostic impact of baseline novel PET/CT metrics including metabolic tumour volume, SUVmax, total lesional glycolysis:
- Collaborators: Both national and international confirmed
- Local PET/CT analysis completed
- Awaiting institutional approval of international collaborator (COVID-19 has impacted on this process)
- Analysis planned for June 2021 with a plan for manuscript submission July/August 2021
4. Assess toxicity & efficacy of nivolumab & rituximab in a prospective phase II clinical trial:
- Trial recruitment completed
- Final analysis completed
- Plan for submission to the May 2021 to the International Conference on Malignant Lymphoma
- Plan for manuscript submission July 2021.

SIGNIFICANCE AND OUTCOMES

1. Due to the paucity of data in G3B FL it was unclear if outcomes we more in keeping with low grade FL (i.e. incurable with a relapsing and remitting course) or analogous to aggressive lymphomas, such as diffuse large B cell lymphoma (i.e. curable). The interim analysis of our data (the largest cohort of G3B FL to date), has shown that G3B FL has superior outcomes to DLBCL but also a more favourable prognostic profile. Despite better outcomes than DLBCL, G3B FL has an ongoing pattern of relapse, similar to low grade FL and as such warrants long term follow-up.
1. As the current practice of visual histological grading has poor concordance, a new objective molecular grading strategy will remove the uncertainty and allow confidence with treatment decisions. Our exploratory/training cohort has delineated grades into distinct groups according to gene expression profile. Testing of our validation cohort is underway.
2. Assessing the prognostic impact of PET/CT metrics in high grade FL has never been determined and will provide essential information for both clinicians and patients.
3. The combination of nivolumab and rituximab in the front-line treatment of FL is associated with favourable toxicity and high response rates providing an alternative to conventional chemotherapy.

PUBLICATIONS / PRESENTATIONS

The excellent outcomes for patients experienced on the 1st FLOR clinical trial has garnered interest for a larger, phase II randomised follow-on study. This is in the planning phase.

ACKNOWLEDGEMENTS

The RACP Foundation will be acknowledged in all publications/presentations that arise out of this body of work.