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FINAL REPORT

Project / Program Title		Precision medicine for resistant chronic myeloid leukaemia
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Award Received		2019 Margorie Hooper Scholarship
Report Date		19 April 2020
Funding Period	Start Date:	14 February 2019
	Finish Date:	31 March 2019

PROJECT SUMMARY

Chronic myeloid leukaemia (CML) is the prototype of a malignancy defined by a single genetic abnormality termed the Philadelphia chromosome, characterized by the formation of the fusion oncoprotein BCR-ABL1. Survival in CML has historically been dismal with the 5-year relative survival in 1995 approximating 35%; allogeneic stem cell transplantation being the only option for long-term survival and prevention of progression to the more advanced stages of CML. The development of targeted agents with marked activity against the BCR-ABL1 fusion protein revolutionized CML therapy ~20 years ago. The introduction of these drugs, known as tyrosine kinase inhibitors (TKIs), have been associated with a dramatic survival benefit; from being virtually incurable in the absence of an stem cell transplant to a life approaching that of the general population; reclassifying CML as a 'chronic disease'. However, despite these advances, patient responses remain heterogeneous. TKI resistance remains a persistent clinical problem.

Based upon our preliminary study, we have identified a number of mutations and genomic variants in CML patients with poor outcomes (blast crisis/multi-drug resistance). The aim of this study is to perform next generation sequencing on patients at the time of diagnosis to identify the number of patients with mutations in addition to BCR-ABL1. Clinical outcome data will be correlated to differentiate which mutations are more likely associated with an inferior outcome.

PROJECT AIMS / OBJECTIVES

Aim:

1. Identify if targeted RNA-based next generation sequencing is an appropriate tool to define the critical genomic lesions associated with resistance in CML

Objective

- To develop an RNA-based targeted gene panel which will be utilised as a comprehensive diagnostic and prognostic tool in CML

SIGNIFICANCE AND OUTCOMES

Despite the excellent progress in managing patients with CML, major challenges remain. Even with our current choice of 5TKIs, 15-20% of patients respond poorly and half of these will die from CML-related causes. To optimise outcomes for CML patients we need to bring CML management into the precision medicine era. This requires detailed assessment of a patient's individual risk profile so that a risk-adapted approach to therapy could be applied. The more potent TKIs reduce the risk of CML transformation and death compared to the first generation TKI imatinib, but overall survival is not improved, presumably because these more potent TKIs lead to greater organ toxicity. It would clearly be preferable to treat lowrisk patients with relatively low cost imatinib and reserve the more potent TKIs for high-risk patients. However, there is currently no accurate and reliable way to determine patient risk with sufficient confidence to be clinically actionable. Furthermore, for a small minority of very high-risk patients, all TKI drugs are ineffective and new approaches are needed, preferably at diagnosis, rather than after resistance or transformation. Identifying mutations that would differentiate poor risk vs optimal outcome patients at diagnosis, will enable a personalized approach to CML therapy.