Personalised Medicine in Haematological Cancers
An Overview

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Types and Prevalence of Haematological Malignancies in Australia

Haematological malignancies, or ‘blood cancers’, include leukaemia, lymphoma, myeloma, or related blood disorders.

The blood is produced in the bone marrow, located in the 'honeycomb' of bone in the pelvis and vertebrae. Within the marrow, the three major components of blood grow - red cells, white cells and platelets; the red cells carry oxygen, the white cells fight infection, and the platelets are a key component of blood clotting.

Cancer by definition is an uncontrolled growth, and the blood cancers are an uncontrolled cancerous growth of the blood cells within body. Illness is caused in this situation due to healthy blood cells being outnumbered, and therefore reducing the body’s ability to transport oxygen, fight infection or clot the blood.

Leukaemias are broadly divided into acute (growing over weeks to months) or chronic (growing over months to years). Leukaemias are classified into four major types, acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML). In adults, the most common forms of leukaemia are AML and CLL, whilst in children the most common form is ALL. In Australia each year more than 2500 people are diagnosed with a form of leukaemia.

The 'second home' of the blood outside the marrow are the lymph glands. The lymph glands act like an 'ant's nest' - trapping and processing infection that enters our body. Lymphomas are cancerous growths that affect the lymphatic system. Normally, a type of white blood cell ('lymphocytes') multiply in response to infection, and then regress when the infection is controlled - much like a heater and a thermostat. In lymphoma, the thermostat is broken and the lymphocytes grow and multiply in an uncontrolled ‘malignant’ manner. Large numbers of these ‘lymphoma cells’ then build up in the glands known as lymph nodes as well as in other parts of the body. Subsequently, the lymphoma cells gradually outnumber the normal lymphocytes, and the ability to fight infection by the immune system is weakened. Lymphomas are classified into either the Non-Hodgkin type (‘B and T- cell lymphomas’) or the Hodgkin type (‘Hodgkin disease’). In Australia each year, around 5800 people are diagnosed with a lymphoma, making it the 5th most common cancer in this country.

Myeloma is a cancer involving the mature lymphocytes, or ‘plasma cells’. These are a type of white blood cell that acts to fight infections by producing highly specialised proteins called antibodies. Myeloma arises when abnormally high numbers of these plasma cells arise within the bone marrow and then subsequently collect in large amounts in other parts of the body, particularly on the surface of various bones. These plasma cells release substances that result in calcium being depleted from bones, thereby making these bones very brittle and prone to breaking. Additionally, the large numbers of the plasma cells within the bone marrow causes a disruption to the development of normal red and white blood cells and platelets, leading to anaemia and a reduction in the body’s ability to fight infection. In Australia each year around 1700 people are diagnosed with myeloma.
Current Treatments for Haematological Malignancies

Similar to other cancers, treatment for the various haematological cancers can be multifaceted, and can include surgery, chemotherapy and radiotherapy. Bone marrow transplantation is sometimes required. The overall aim of these treatments is to kill the causative cells for each of the malignancies, and thereby induce ‘remission’ - the state in which malignant cells are not detectable in the blood stream, bone marrow, lymph nodes, bone or other affected organs.

Subsequent to remission, additional ‘maintenance’ treatment is often required to prevent any ‘residual’ disease causing a re-establishment of the original disease, referred to as ‘relapse’. As suggested by their classification, ‘acute’ forms of disease require more urgent and intensive treatment, without which mortality can be very high, as compared to ‘chronic’ forms, which can sometimes require monitoring before progressing to more aggressive treatment.

Future Treatments for Haematological Malignancies

Over the years we have made major advances in the treatment of cancers including the blood cancers. We now consider the 'pillars' of killing cancers.

The diagram above demonstrates that the 3 'classic' pillars are surgery, radiotherapy and chemotherapy. The major advances (in the last 10 years in particular) are 2 additional 'pillars' for killing cancer - precision therapy and immunotherapy. Notably, these 5 pillars are not separate and often interlink. Immunotherapy is a strategy whereby we try to harness the immune system to help fight blood cancer. Epworth Healthcare is investing significant resources into researching and providing state-of-the-art immunotherapy and precision therapy to patients. Indeed, the establishment of the department of Molecular Oncology and Cancer Immunology demonstrates this commitment and priority focus.
The Advent of ‘Personalised Medicine’ in Cancer Treatment

The utilisation of surgery, chemotherapy and radiotherapy (classic pillars) has brought about the ability to induce long-term remission and survival in a variety of haematological malignancies. However, there remains the situation in which some individuals do not respond as well as hoped, in particular to chemotherapy. We continue to be unable to answer the question - why do some individuals with a blood cancer that looks identical 'down the microscope' get cured, whilst other individuals fail to respond or relapse?

In this regard it has become increasingly recognised that the different subtypes of haematological malignancies are likely to be more genetically complex than initially thought. This realization has been borne out by the ability of modern high resolution genetic and molecular biology techniques to detect mutations that are very different between individuals even if their cancers appear identical with standard pathology testing.

This ability has led us to understand that each individual’s cancer is likely to have come about as a combination of various genetic mutations, including those that are 'germ-line' (inherited) or that occur during the evolution of the cancer, ‘somatic mutations’. Thus, each individual’s cancer is likely a ‘genetic fingerprint’ specific for that individual, in which many of the genetic mutations would be the same as those in another individual, but others would be unique to that individual.

Two major landmarks in our understanding have led to our capacity to tackle the challenge of genomically profiling individual's cancers:

- Firstly, the sequencing of the human genome and we now know all the genes humans have; and
- Secondly, computer technology that can now analyse terabytes of information in a timely fashion.

Thus, we are currently in an era where we have the potential to genetically fingerprint an individual's cancer - undertake molecular analysis of the tumour cells at diagnosis and at times of relapse.

Moreover, a third major step forward has been advances in drug development - where new 'designer drugs' can be chemically produced based on 'sub-atomic' studies (i.e. the Synchnatron) that identify the structural targets that drugs need to 'hit'. This makes possible the use of a much more 'targeted therapies' approach whereby particular genetic mutations can be targeted with drugs specific for these mutations. This forms the basis of a ‘personalised medicine’ approach to cancer therapy - the 4th pillar.
The next step in genomic personalised blood cancer therapy
- circulating tumour DNA

At the same time it has been very recently demonstrated that within the bloodstream there is genetic material that has 'leaked out' from a person’s malignancy; this genetic material is referred to as ‘circulating tumour DNA’ or ‘ctDNA’. Indeed, the detection and analysis of ctDNA has multiple significant clinical implications for the treatment of patients with haematological malignancies:

- It can establish a diagnosis earlier when malignant tissue can be difficult to obtain;
- Often a cancer can be like an 'iceberg' where there can be lots of information hidden and not fully obtainable with a biopsy from a single site - obtaining ctDNA can provide a much more comprehensive overview of the genomic landscape of the malignancy as a whole without having to perform potentially multiple invasive biopsies;
- If multiple mutations are found, these can be targeted earlier and increase the potential for cure;
- Critically, this non-invasive assessment can be continued over time to monitor a patient’s response to treatment and thus guide more precise therapy. Indeed, it can help determine when to stop therapy (when the ctDNA disappears) or to alter therapy (if the ctDNA fails to be eradicated despite standard therapy); and
- Finally, it can also allow for much earlier detection of relapse, and therefore allow for earlier institution of salvage therapy.

However, this area of research is still very immature and the challenges ahead are to determine the balance between accurately detecting these low levels of ctDNA without producing 'false-positive' inaccurate results.

We are fortunate in Melbourne to have world-leaders in this area who can work together to address the role of ctDNA analysis to help manage patients with haematological cancer.

Already, we have teams in Melbourne that are producing important laboratory results in tumours such as leukaemia, lymphoma and breast cancer. However, such results have to be translated into the clinic and we anticipate with a collaborative effort such strategies will be available in the clinic in the next few years. Our aim is to use the strength of this team to develop and validate ctDNA-based assays that can subsequently be used in routine clinical genomic testing for haematological malignancy, and thus provide a personalised molecular medicine strategy at the Epworth Hospital and Victorian Comprehensive Cancer Centre (VCCC).

Infrastructure established to date

We have a long-term strategy to bring personalized medicine to Victorian patients with blood cancer - lymphoma, myeloma and leukaemia. Our aim is to have a focused approach to comprehensively genetically analyse all patients with blood cancers. Moreover, we know we can 'cross-fertilise' across the different blood cancers, with the knowledge we gain along the way.
We will work closely with our collaborative partners in Victoria (particularly PeterMac and the VCCC), nationally and internationally.

**Step 1:** Establishing a Genomics Platform for Myeloma: In 2013 we established the myeloma genomics project at VCCC which was funded by Snowdome Foundation for approximately $4.1M. This has established an infrastructure for tissue collection, comprehensive genomic analysis, curation and reporting.

**Step 2:** Broadening that Platform into other blood cancers: In the last 2 years, this funding has been leveraged to allow testing of patient material at PeterMac/VCCC for most blood cancers - leukaemia, lymphoma and myeloma. However, the funding is insufficient to test all patients, nor to develop better and faster techniques for standard genomic testing. The leukaemia program is growing and will require additional funding in the next few years.

**Step 3:** Turbo-charging lymphoma genomics: In 2016, the Snowdome Foundation obtained a generous donation from the Wilson Family to establish a lymphoma genomics centre at the VCCC. This $5.5M will be utilised to expand the techniques used, speed the process and increase the number of specimens that can be tested. It will provide key technologies that can be applied to proposed ctDNA initiative.

We are currently in discussions with the Victorian Department of Health to look at opportunities for additional government funding particularly in the context of pharmco-economic modelling of these new technologies.

**Step 4:** Developing cutting-edge CtDNA research strategies: The myeloma and lymphoma platforms already being established at the VCCC provide an enormous resource base for the proposed ctDNA proposal; the techniques are already being evaluated to see how they best apply to assess ctDNA in the clinical setting. The methodologies are similar, the analysis is similar and the team is already assembled.

Epworth, being Victoria’s largest provider of cancer services will be a major contributor to this initiative. It will provide patient specimens and substantial resources to this project. Specifically, Epworth has already committed to two full-time scientists to work at the VCCC genomics laboratory and we have committed funds to a shared Epworth-VCCC Haematology Fellow to oversee the ctDNA programme in 2016/17.

In addition, Epworth also sees opportunities to explore genomics ctDNA in areas beyond blood cancers. We have just established a joint Walter & Eliza Hall Institute/Epworth Fellowship for 2017 focusing on genomic research in gastrointestinal, breast, gynaecological and prostate cancers and in 2018 plan to extend that to other cancers including lung. We will further appoint specimen and data collection curator and research assistants and also implement a new medical informatics system which will integrate into international genomic efforts particularly in the USA.
Our Need

We will be seeking support to develop Step 4 - developing cutting-edge CtDNA research strategies. This is a $3 million project being fundraised by Epworth. To this end, we have been fortunate to have built a funding partnership with Snowdome Foundation who will source $1.3 million towards the project.

We wish to seek multi-year support from the Phyllis Connor Memorial Trust and other Equity Trustees managed trusts to support the appointment of two scientific staff being:

1. Full time Tissue Curator who will work across Epworth and VCCC sites managing the secure extraction, storage and transport of patient biopsies (Ct-DNA) from Epworth to the VCCC @ $80,000 per annum x 3 years; and

2. One of two Laboratory research assistants to analyse samples collected from Epworth patients @ $60,000 per annum x 3 years.

Our Objectives for the CtDNA project

**Aim 1:**
Develop, optimise and validate ctDNA-based assays (including complementary genomic techniques) to be used in the detection and monitoring of ctDNA in B-cell malignancies (including lymphoma and myeloma) to a diagnostic standard in a National Assessment of Testing Authorities (NATA)-accredited laboratory (note: such accreditation is necessary to implement these methodologies into standard clinical practice). Subsequently, to implement these assays as part of the routine clinical genomic testing offered through the Molecular Haematology Laboratory at VCCC which is partnering with the Epworth Genomics Centre.

**Aim 2:**
To perform novel cutting-edge studies examining the utility of ctDNA detection in B-cell malignancies to inform clinical decision making. We plan to utilise samples collected from patients who are already part of a study we are undertaking as part of an existing larger project. This larger project is part of the 'lymphoma flagship' funded by the Melbourne Genomic Health Alliance (MGHA). Such flagships address the potential use of genomics across various areas of health care (epilepsy, pre-natal testing, and undiagnosed genetic disorders) and members of this application are key-investigators on the lymphoma flagship which is addressing how whole exome sequencing (WES) can be utilised to improve the diagnosis and management of patients with high-risk lymphoma. We will use specimens from the flagship study which have already been 'highly molecularly defined' to assess ctDNA as well.

**Aim 3:**
To offer testing to patients with B-cell malignancies (lymphoma and myeloma) treated at Epworth/VCCC as part of standard genomic workup, and to perform translational research (Dawson lab at VCCC) using the patient samples and the samples acquired from the lymphoma flagship.