Improving early diagnosis and treatment of haematological cancers

The haematological cancers are the only cancers where the matrix in which the tumour cells reside is accessible without a biopsy. Coupling this with the maturation of longitudinal serum banks allows the study of biomarkers and targets in pre-disease samples and of the development of disease from a healthy state through to cancer formation. Such studies could support earlier diagnosis and treatment, which may ultimately improve survival, write *Drs Mike Fisher* and *Wendy Alderton* of Abcodia

Haematological cancers are a very diverse group of diseases that originate in the bone marrow and lymph nodes. They affect people of all ages, but with greatest incidence amongst the elderly. The prognosis and responsiveness to treatment of these conditions also varies very widely.

The haematological cancers are split into 3 types: the leukaemias (30% of total blood malignancies), the lymphomas (56%) and the myelomas (14%). Together, they make up nearly 10% of new cancer cases in the USA each year and, sadly, incidence rates for these cancers as a group are rising.

An extremely important aspect of developing diagnostics and treatments for the blood cancers is determining their pathophysiology, that is, how they initially form and then progress. However, there remains much more to be understood about how this actually happens in the human body as it is quite difficult to closely (or indeed prospectively) study the biology of individuals from a healthy state through to the development of a cancer. Instead we rely on model systems and extrapolate their results to what might happen in humans. An unfortunate result of these factors is that we tend to diagnose these diseases only when they become symptomatic. Similarly, this restricts drug development to targets related to symptomatic and later-stage diseases, using animal models and cell lines derived from tissue that may already have experienced significant disease progression.

A better strategy would be to find biomarkers or druggable targets within pre-symptomatic tissue (e.g. early progenitor cells) which would not only allow early diagnosis but would enable a resulting drug to be positioned as a front-line therapy. This would clearly improve both diagnosis and treatment options, giving patients more choices, enabling them to recover more rapidly and reducing the chances of remission. Such a treatment would also be more likely to achieve better health-economic assessments, which are more difficult for therapeutics that provide only a limited extension of life. There is some good news in this area – GSK/Genmab have just announced positive results for Arzerra (ofatumumab), which is indicated as a frontline therapy for chronic lymphocytic leukaemia (CLL), but more could be done across the healthcare industry to improve diagnosis and treatment of the haematological cancers.

Interestingly, unlike solid tumours, blood samples can provide effective access to the medium in which the diseased tissue resides. This allows a greater ability to study the disease, in comparison to some of the solid tumours for which it is only ethical to obtain a biopsy sample during diagnosis of symptomatic patients, or from patients already diagnosed with the disease. Clearly, taking biopsies regularly from the organs of healthy people to study disease formation would be impossible.

The maturing of a number of longitudinal biobanks, such as those derived from the UK Collaborative Trial in Ovarian Cancer Screening (UKCTOCS) now allow the study of pre-cancerous patient samples to discover markers and targets that may change much earlier in disease progression.

Although there is an easier diagnosis method for these cancers due to blood being readily accessible, there is still a significant unmet need for early diagnosis and treatment. An early action in the diagnostic process is often to simply watch and wait – early disease signals don't always translate into full-blown disease. However, as with all cancers, early intervention can significantly improve outcomes. Once identified, treatment can consist of bone marrow transplants and/or chemotherapy. However, the current agents available can lack efficacy or have significant side effects – better therapeutics are needed. Among the top research-based pharmaceutical companies, there are 57 clinical trials in these diseases, highlighting the unmet medical need (see Table 1). However, few of these trials are targeting front-line therapy, due to the difficulties of discovering and developing drugs that can provide significant improvements over the existing standard of care.

On the other hand, a number of haematological malignancies are often preceded by a diagnosable 'pre-cancerous' syndrome. For example, myelodysplastic syndrome (MDS) is often a precursor of acute myelogenous leukaemia (AML). However, some cases of MDS do not go on to develop AML, and some AML cases develop in the absence of MDS (or the patients are not diagnosed with the syndrome). Thus, biomarkers for improved diagnosis of MDS which could identify those cases that progress to AML would have high clinical utility.

Another example is monoclonal gammopathy of unknown significance (MGUS) in relation to multiple myeloma. MGUS is even less likely to be formally diagnosed ahead of multiple myeloma, and so it is unclear whether there is a direct transition between the two diseases or whether MGUS is simply a risk factor for the subsequent neoplastic disease.

The availability of pre-diagnosis samples for these diseases, thanks to

significant investments in large-scale screening trials, now offers a valuable opportunity to understand early disease formation, particularly with blood cancers. Human serum carries a significant number of molecules, from molecular markers such as DNA, RNA and miRNA, to proteins and small molecules produced by diseased cells and tissues – many such markers can be used to study disease formation and progression. Fortunately, some biobanks have collected samples from large populations over a number of years and now hold enough longitudinal pre-diagnosis samples to enable meaningful studies to be performed. The key now is to utilise these sample banks effectively to ensure we gain a greater understanding of the various biomarkers affected by these diseases, and how changes in these biomarkers translate to pathological states and disease progression. The key here is not to develop knowledge for knowledge's sake, but to develop truly innovative diagnostics and therapies that make a difference to clinical practice.

Table 1. Adult haematological cancer drugs under development in the major pharmaceutical companies

Drug name	Company	Disease	Phase
Abemaciclib	Bayer	hematological cancer	I
ABT-888	AbbVie	multiple myeloma	I
Afuresertib	GSK	multiple myeloma	I
AMG 319	Amgen	Hematologic malignancies	I
Anti-CXCR4	BMS	hematological cancer	I
AZD1208	Astrazeneca	haematological malignancies	I
AZD9150	Astrazeneca	haematological malignancies	I
Blinatumomab	Amgen	Acute lymphoblastic leukemia/Non-Hodgkin's Lymphoma (NHL)	III
Carfilzomib	Amgen	multiple myeloma	III
Cetuximab	BMS	hematological cancer	I
CRL019	Novartis	Leukemia	Pre-submission
daratumumab	Janssen	multiple myeloma	III
Denosumab	Amgen	Cancer-related bone damage in patients with multiple myeloma	III
Eltrombopag	GSK	acute myeloid leukaemia	II
Ibrutinib	Janssen	Chronic Lymphocytic Leukemia/Mantle Cell Lymphoma/Indolant Non-Hodgkins Lymphom	III (EU), filed 4/14 (US)
inotuzumab ozogamicin	Pfizer	Non-Hodgkin lymphoma	III
JAK2 Inhibitor	BMS	hematological cancer	I
LBH589	Novartis	multiple myeloma	Pre-submission
MEDI-551	Astrazeneca	haematological malignancies	I
MLN8237(alisertib)	Takeda	Non-Hodgkin lymphoma	I
Moxetumomab pasudotox	Astrazeneca	hairy cell leukaemia	II
NCT00275262	AbbVie	Hodgkin Disease Lymphoma, Non-Hodgkin Multiple Myeloma	II
NCT01239797	AbbVie	multiple myeloma	III
NCT01335399	AbbVie	multiple myeloma	III
NCT01393964	AbbVie	multiple myeloma	I
NCT01441973	AbbVie	Smoldering Multiple Myeloma	II
NCT01478048	AbbVie	multiple myeloma	II
Notch Inhibitors	BMS	hematological cancer	I
Obinutuzumab	Roche	non-Hodgkin's lymphoma	III
Ofatumumab	GSK	lymphoma, chronic lymphocytic leukaemia	III
PF-04449913	Pfizer	AML	II
RG7601	Roche	lymphoma	II
RG7741	Roche	lymphoma	I
RG7845	Roche	hematological tumors	I
Rituximab	Roche	non-Hodgkin's lymphoma	filed 2012 EU
SAR245408	Sanofi	Lymphoma	I
SAR245409 (XL765)	Sanofi	Lymphoma/leukemia	II
SAR3419	Sanofi	Non-Hodgkin's lymphoma	I
SAR3419	Sanofi	Lymphoma/leukemia	II
SAR393590	Sanofi	Hematologic malignancies	I
SAR650984	Sanofi	Multiple myeloma & CD38+ hematologicmalignancies	I
SGN-35 (brentuximab vedotin)	Takeda	Hodgkin lymphoma/T-cell lymphoma	III
Tabalumab	Bayer	multiple myeloma	II
TGFβR1	Bayer	hematological cancer	II
Volasertib	Boehringer Ingelheim	Acute Myeloid Leukemia (AML)	III