RARE HAEMATOLOGIC MALIGNANCIES: BAD DISEASES CAN HAVE GREAT OUTCOMES WHEN THE RIGHT TREATMENTS ARE DISCOVERED

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Abstract

Individual haematologic malignancies are uncommon when compared to solid tumours. Careful definition of distinct subtypes of leukaemias and lymphomas by marrying clinical characteristics with distinct morphological and genetic features has greatly advanced understanding of pathobiology, leading to novel treatments and improved prognoses of different leukaemias and lymphomas. We examine the success stories of acute promyelocytic leukaemia and chronic myeloid leukaemia, and explore how next generation sequencing will empower translational research and treatment advances for rare haematologic malignancies.

Introduction

While haematologic neoplasms account for approximately one-sixth of all non-cutaneous cancer diagnoses, each individual type of blood cancer is uncommon. The incidences of acute myeloid leukaemia (AML), non-Hodgkin lymphoma and Hodgkin lymphoma were 4, 20 and 2.7 cases per 100,000 respectively in the US in 2011.[1] In contrast, 140 new diagnoses of prostate cancer and 130 new diagnoses of breast cancer per 100,000 were made in the same year. Haematologic neoplasms are markedly heterogeneous, with more than 35 subtypes of acute leukaemias, 35 subtypes of non-Hodgkin lymphoma and six subtypes of Hodgkin lymphoma currently recognised.[2] Each individual subtype of haematologic neoplasm can therefore be considered a rare disease. However, this has not prevented significant advances from being made in understanding the pathobiology of these diseases and in their treatment. Paradoxically, the rarity has facilitated scientific advancement, by enabling focus on their distinctive morphologic, cytogenetic and molecular characteristics to develop targeted therapies. In this article, we will review how two rare leukaemias with poor prognoses when treated with cytotoxic chemotherapy, are now considered to have very favourable prognoses with targeted therapies.

Acute promyelocytic leukaemia

Acute promyelocytic leukaemia (APL) is a subtype of AML, with an incidence of 0.27 cases per 100,000 per year and no difference in frequency between age groups.[3] APL as a distinctive disease was first described in 1957 by Hillestad.[4] The patients presented with bleeding diathesis and died within hours to six days of hospital admission from disseminated intravascular coagulopathy. Hillestad presciently described APL as "… the most malignant form of acute leukaemia."

APL is characterised by an excess of abnormal promyelocytes with prominent Auer rods in the bone marrow. In classical APL, only occasional aberrant promyelocytes may be found in the peripheral blood. A variant form of APL with hypogranular promyelocytes, also known as 'microgranular' APL, presents with a higher promyelocyte count in the peripheral blood. In the late 1970s, the French-American-British Co-operative Group classified APL and 'microgranular' APL as M3 and M3 variant respectively.[5,6] The ability to identify APL by morphology is crucial for early diagnosis and treatment of this deadly disease. This is supplemented by APL's specific cytogenetic and molecular abnormalities (described below).

Daunorubicin was the first chemotherapeutic agent effective in treating APL, achieving complete remission (CR) in 58% of patients with decreased bleeding complications.[7] The addition of cytarabine increased CR to 68-72% but median duration of CR remained short at only 24 months.[8,9]

It was hypothesised that APL could be due to a defect that prevents promyelocytes from differentiating to more

mature granulocytes. After Breitman et al showed that all-trans-retinoic acid (ATRA) induces differentiation in an APL cell line (HL-60) and APL cells obtained from patients, the clinical efficacy of ATRA was first shown by the Chinese in 1988, when all 24 patients given ATRA monotherapy achieved CR.[10-12] Within 10 years, ATRA plus chemotherapy had become the gold standard, and four year disease-free survival had increased from <40% to 71-93%.[7,9,13-15]

At the same time, arsenic trioxide was also introduced for the treatment of relapsed APL. Arsenic alone resulted in CR in 85-90% of patients.[16-18] In a subsequent study, arsenic in combination with ATRA resulted in rapid and safe induction of remission with no relapses.[19] Most recently, in a randomised trial, the two-year overall survival for patients treated with ATRA and arsenic was 99%, compared to 91% in patients treated with ATRA and chemotherapy.[20] APL may be the first cancer where cytotoxic therapy can be safely replaced with a combination of a vitamin and a mineral in order to affect a cure in nearly all patients.

The success in treating APL is related to its molecular pathogenesis. It was recognised early that APL cells had a translocation between chromosomes 15 and 17,[21,22] t(15;17)(q21;q22) that fuses the PML on chromosome 15 with RARα on chromosome 17.[23,24] The PML-RARα is measured using reverse transcriptase polymerase chain reaction (RT-PCR) allowing early detection of relapse. The chimeric protein exerts a negative effect on the normal function of PML and RARα proteins, disrupting cellular processes, including granulocytic differentiation.[25] The constant incidence of APL over different age groups suggests that APL has a single rate limiting mutation, namely PML-RAR.[26] Arsenic and ATRA work by binding to the PML and RARα moieties respectively, thereby causing degradation of PML-RARα and allowing differentiation of the promyelocytes, and extinction of the leukaemic clone.

In five decades, APL has changed from an invariably deadly disease to a highly curable one. While the revolution in treatment occurred prior to our comprehensive understanding of the molecular pathogenesis of the disease, the use of molecular assays enabled minimal residual disease to be used as a validated surrogate for cure, accelerating the development of clinical algorithms. The current challenge is to translate the lessons learned from APL to other forms of acute leukaemia.

Chronic myeloid leukaemia

Chronic myeloid leukaemia (CML) ideally exemplifies how understanding the biology of a rare cancer enables the development of a targeted therapy that revolutionises care and clinical outcomes. The incidence of CML is estimated to be 0.6 to 2 per 100,000 per year, with a median age at diagnosis of 60 to 65 years.[27,28] More than 90% of patients present in chronic phase CML with splenomegaly and leukocytosis. CML is diagnosed by identifying its pathognomonic peripheral blood features of basophilia, eosinophilia and granulocytes in various stages of maturation and by confirming the presence of the fusion oncogene, BCR-ABL.[2]

In 1960, Nowell and Hungerford reported the presence of a 'minute' chromosome in seven cases of CML. In 1973, Rowley demonstrated that the Philadelphia chromosome consisted of a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)).[29] In subsequent research, this translocation was shown to involve the ABL oncogene on chromosome 9 with a small breakpoint cluster region (BCR) on chromosome 22.[30,31] The chimeric bcr-abl mRNA encode a protein with increased tyrosine kinase activity compared to wild-type ABL.[32-35] BCR-ABL was shown to be pivotal in leukaemogenesis when expression of BCR-ABL in mice induced phenotypes resembling CML.[36,37]

Treatment prior to 2000 comprised interferon or hydrea, but this rarely changed the natural history of the disease. Over several years, patients would progress from chronic phase CML to accelerated phase and then to a blast crisis that resembled acute leukaemia. Allogeneic haematopoietic stem cell transplant is potentially curative in 70-80% of younger patients, but requires a compatible stem cell donor, a medically fit patient and an acceptance of risks of transplant-related mortality and long-term morbidity.[38] Therefore, better therapies were required and BCR-ABL was an attractive target given its role in the pathogenesis of CML.

In pre-clinical studies, a tyrosine kinase inhibitor (TKI), STI 571 (imatinib), inhibited the proliferation of cell lines expressing BCR-ABL and reduced tumour formation in mice.[39] Imatinib also decreased the formation of BCR-ABL colonies from peripheral blood and bone marrow samples of patients with CML by 92-98%. Imatinib did not inhibit the formation of normal colonies from the patient samples, demonstrating the specificity of the compound to BCR-ABL. A phase I clinical trial of imatinib commenced in 1998 on patients with chronic phase CML who were resistant to interferon therapy; 53 of 54 (98%) patients achieved complete haematologic response without significant toxicity.[40] These findings were confirmed in additional trials and in 2001, imatinib was approved by the Food and Drug Administration for use in CML.[41-44]

Long-term follow-up of the randomised trial revealed that 93% of newly diagnosed patients treated with imatinib remain alive and progression-free after six years.[45] Allogeneic stem cell transplantation is now rare for CML, whereas in 2001, CML was the most common indication for the procedure. Molecular monitoring of BCR-ABL transcripts in the blood is standard, and enabled intervention with second generation TKIs

(dasatinib, nilotinib and ponatinib) where imatinib resistance due to well recognised mutations in ABL are observed.[46,47] Imatinib and other same-in-class drugs (dasatinib, nilotinib, ponatinib) have transformed CML into a truly 'chronic' disease, controlled with a daily tablet. Further, in patients with undetectable minimal residual disease (using sensitive RT-PCR measurement of BCR-ABL transcripts), it may even be appropriate to stop imatinib, with 40% of patients remaining disease-free off therapy.[48,49]

Research questions remain on the optimal duration of treatment, the choice between various TKIs as optimal first and second line therapy, and the care of the now rare patient with CML in blast crisis.

Future for other rare haematologic malignancies – the era of next-generation sequencing

Recently, improvements and widespread adoption of next generation sequencing (NGS) have enabled us to sequence and analyse genetic material with ease and at a reduced cost. NGS promises to revolutionise research and management of haematologic malignancies.[50] The ability to perform whole genome sequencing of an individual patient's neoplasm has already identified recurring mutations in previously unsuspected genes e.g. IDH1 and DNMT3A in AML.[51,52] As AML is broken down into 25-35 subtypes, grouped according to their underlying driver mutations, the field anticipates the development of new treatment approaches for each.

While for APL and CML, it took decades to understand the basic cytogenetic and molecular mechanisms of the disease and develop pathobiology-specific therapies, for AML and other haematologic neoplasms, NGS promises to accelerate these timelines to mere years. The challenges of the 21st century will be in understanding the data generated from NGS and applying it to individual patient care. In this area, haematologic neoplasms will likely to continue to blaze a path.

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