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HAEMATOLOGICAL MALIGNANCIES - INTRACTABLE OBSTACLES AND PATH FINDING BREAKTHROUGHS OVER 40 YEARS

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Abstract

Haematological malignancies have identified the path forward for oncology, initially with systemic treatment and combination chemotherapy and limiting the need for or extent of radiotherapy. In recent years, important targeted therapies were first demonstrated as practical with the first tyrosine kinase inhibitors, the first monoclonal antibodies and the extensive genetic characterisation and classification of these diseases. The genomic era holds the promise of further, more rapid progress, with remaining intractable problems such as poor outcomes overall with acute myeloid leukaemia, both primary and secondary, and possibly new therapy that could avoid the short and long-term side-effects of curative chemotherapy. The extensive sub-classification of leukaemia and lymphoma into smaller sub-sets have made some large scale clinical trials a challenge and may have flagged an emerging obstacle to progress in cancer trials more generally.

During the past four decades, significant progress has been made in identifying the molecular pathogenesis of lymphomas as a clonal expansion of B cells, in the majority, and of T cells. Similarly, our understanding of leukaemia has increased dramatically with the identification of the genetic abnormalities fundamental to the disease process. Such knowledge has led to major breakthroughs in the classification and treatment of these diseases.

Chemotherapy in the beginning

While Paul Ehrlich first coined the phrase 'chemotherapy', modern systemic therapy was ushered in by the serendipitous observation that accidental exposure to mustard gas caused bone marrow failure. The resulting application of alkylating agents and combination chemotherapy to leukaemia and lymphoma in clinical trials had early success, leading to the promise of cures in these diseases and decades of progress in cancer.

In reality, there has been good progress in lymphoma and childhood leukaemia, but many other cancers have quickly surpassed gains in acute myeloid leukaemia (AML) in the modern era. In Australia, five year survival from AML was around 10% in the late 1980s, and remains only 24% currently, although some sub-sets do better.[1] In contrast, Hodgkin's disease has a five year survival of 88%, non-Hodgkin's lymphoma (NHL) 71% and all cancer 66%.

Standard induction therapy for AML remains based on anthacycline and cytarabine, with seminal trials of high dose cytarabine induction conducted in Australia.[2] Major advances in AML have included understanding of the importance of genetic changes for classification and prognosis, use of all-trans-retinoic acid in acute promyelocytic leukaemia,[3] and haematopoietic stem cell transplantation. Targets for future advances could include mutations in FLT3, RAS and other genetic mutations affecting cellular pathways that confer a proliferative or survival advantage for leukaemia cells. Another set of mutations associated with improved differentiation and self renewal could be subject to all-trans-retinoic acid or histone deacetylase or other inhibitors. Haematopoietic stem cell transplantation offers the possibility of cure to individuals, especially in first complete remission. Use of risk stratification based on initial genetic profile and subsequent post-induction bone marrow examinations has been an important area of progress in haematopoietic stem cell

transplantation. It is expected that future whole genomic analysis should take this field forward more quickly, with a more sophisticated approach to risk and therapy than the three levels of risk often used, and with the identification additional druggable targets for treatment.[4]

Targeted therapy

Chronic myeloid leukaemia (CML) is a haemopoietic stem cell disease. Historically, CML patients progressed to blast crisis and death at a rate of around 5-10% per year in the first two years, increasing to 20-25% per year in subsequent years. The majority of genetic changes in progression occur in the transition from chronic phase CML to accelerated phase. CML is one of the first and best examples of the promise of personalised or precision therapy in oncology. The discovery of the Philadelphia chromosome or translocation t(9:22) in 1960, led to an understanding of the central role of the chimeric gene BCR-ABL in the pathogenesis of CML in the 1980s. The function of BCR-ABL is dependent on its tyrosine kinase activity, making it an ideal target for tyrosine kinase inhibitors (TKI). The TKI imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase above and was a major breakthrough in CML, increasing overall survival to around 89%, with only 7% progressing to blast crisis after five years.[5] New TKIs, dasatinib and nilotinib, have been developed for imatinib resistance or intolerance and dose escalation of imatinib developed for resistance. Newer TKIs include bosutinib and ponatinib for specific BCL-ABL mutations of T3151. This approach has shown the promise of TKIs for use in other malignancies. Despite these successes, allogenic haemopoietic cell transplantation remains the only therapy to durably eradicate this disease, offered after assessment of response to TKI therapy. Future advances may occur by targeting processes downstream from BCL-ABL, including P13-kinase, RAF and MEK. An important ongoing area of work is the best approach to minimal residual disease in CML.

The rapid early progress in lymphoma with combination chemotherapy above was not matched by progress in the 1980s and early 1990s. However, the importance of new classifications, better prognostic tests and a better defined, more limited role for radiation were important improvements. Recent advances in NHL include an understanding that chromosomal translocations are important characteristics of NHL. The presence of proto-oncogenes in proximity to chromosomal translocation sites have changed the expression of the proto-oncogene. Examples include the translocation involving BCL6 in diffuse large B cell NHL and less commonly t(11:18) in mucosa associated lymphoid tissue (MALT) NHL, providing possible new targets for therapy.

Use of monoclonal antibodies

The development of therapeutic monoclonal antibodies was pioneered in lymphoma with rituximab directed against CD20, the first such antibody approved by the Food and Drug Administration in the US in 1997. Such antibodies are therapeutic through a range of mechanisms, including cell-mediated cytotoxicity, complement-dependant cytotoxicity and immunomodulation. The impact of rituximab in addition to chemotherapy was shown in a number of clinical trials across a range of lymphomas.[6] This novel approach has been followed by other therapeutic anti-bodies in oncology practice, including trastuzumab targeting HER2 in breast cancer (1998), alemtuzumab targeting CD52 in chronic lymphocytic leukaemia (2001), cetuximab targeting EGFR in head and neck cancer (2001) and bevacizumab targeting VEGF in colorectal cancer (2004). Recent developments have also included the approval of immuno-conjugates such as gentuzumab targeting CD33 in AML (2000), and ibritumab targeting CD20 in NHL (2002). Newer approaches include single agent bendamustine plus rutuximab in indolent lymphomas.[7]

Conclusion

Major advances in haematological malignancies have occurred following the early adoption of research innovation now relevant more generally in oncology. Intractable obstacles remain, with the opportunity for more rapid progress based on insights from genomics.

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