Cancer Treatment in the Era of Targeted Therapy: the March is on!

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Editor

In general, cancers including haematological cancers are characterised by either of the following three mechanisms: 1. activation of oncogenes; 2. loss of function of tumour suppressor genes or 3. inhibition of cellular differentiation. Oncogenes confer proliferative or survival advantages while tumour suppressors normally prevent development of cancer by activating apoptosis. Therefore, cancer cells often have constitutive activation of oncogenes together with inactivation of tumour suppressor genes. On the other hand, failure of proper differentiation of precursor cells may result in cancers.

Haematological cancers comprise cancers arising from lymphoid (lymphoma, acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and multiple myeloma) or myeloid origin (acute myeloid leukaemias [AML] and chronic myeloid leukaemias [CML], myelodysplastic syndrome). Many either arise from progenitors or stem cells that are naturally residing in the bone marrow or metastasise to the bone marrow (lymphoma, multiple myeloma). On the other hand, solid cancers arise from transformed epithelium including carcinomas of the breast, lung, liver and colon.

Basic research has enormously impacted the modern management of both haematological and solid cancers. Because of the understanding of the molecular pathogenesis of cancers that usually involve concomitant activation of oncogenes and inactivation of tumour suppressor genes, numerous therapeutic targets have been identified in the last 2 decades. For instance, imatinib, a tyrosine kinase inhibitor, is the first small molecule found to inhibit the pathogenic fusion gene, BCR/ABL, which is the primary oncogenic event in chronic myeloid leukaemia. Indeed, since the first randomised controlled trial, the International Randomized Study of Interferon and STI571 (IRIS) trial, published in 2003, which showed a much higher rate of response (both haematological and cytogenetic) in CML patients randomised to receive imatinib. Moreover, a substantial number of patients receiving imatinib may actually achieve molecular remission, which has been a mission impossible with conventional chemotherapy. Indeed the updated survival for patients enrolled in that trial showed the 8-year overall survival is 80% in patients receiving imatinib, which is comparable or superior to survivals achieved by the use of allogeneic haematopoietic stem cell transplantation in young CML patients transplanted with stem cells from an HLA-identical sibling. Because of the significant response rate including molecular remission and the remarkable survival associated with the use of imatinib, allogeneic HSCT is no longer the first line therapy in CML patients but reserved for patients with accelerated phase or blastic transformation. Moreover, while intensive chemotherapy or allogeneic HSCT is only applicable in relatively young patients, imatinib and many other targeted therapies are generally non-myelotoxic or minimally myelotoxic, and hence can be used in both young and elderly patients alike. Therefore, the scale of impact of the advent of targeted therapy has been enormous, and the momentum is still on. Other major targeted therapies in haematological cancers include the monoclonal antibodies such as rituximab and alemtuzumab, and small molecules like bortezomib, which is an nuclear factor kappa B inhibitor and very effective in the treatment...
of myelomas and lymphomas. Moreover, epigenetic therapy has come of age too. Epigenetics refers to the alteration of gene expression not associated with gene mutation but due to either promoter DNA methylation or histone modifications at the promoter regions of tumour suppressor genes. Demethylating therapy such as 5-Azacitidine (Vidaza) or Decitabine (Dacogen) is now the choice of therapy in patients suffering from myelodysplastic syndrome, a disease of the elderly characterised by peripheral cytopenia and a propensity of leukaemia transformation. Indeed, 5-azacytidine has been shown to result in less transfusion requirements, increased response rate, and hence better quality of life. Moreover, it also suppresses leukaemia transformation, and hence improves overall survival.

Similar advances have been made in solid cancers too. For instance, therapeutic antibodies have emerged as an important part of treatment in multiple solid cancers. In breast cancer, trastuzumab is a welcome addition to the treatment of HER2-overexpressing breast cancers. In colorectal cancer, cetuximab, an inhibitor of EGFR signalling, has been shown to be useful in metastatic colorectal cancers and head and neck cancers. Similarly, small molecules have made substantial impact in cancer therapy too. For instance, in bronchogenic carcinoma, the era of targeted therapy has come for the treatment of non-small cell lung cancers, best exemplified by the story of epidermal growth factor receptor inhibitors like gefitinib (Iressa) and erlotinib (Tarceva) in addition to anti-angiogenesis. Moreover, the future of lung cancer treatment will certainly rest on a personalised approach with more molecularly targeted agents on the horizon. Finally, in hepatocellular carcinoma, a cancer highly associated with hepatitis B infection, which is a prevalent disease in Hong Kong, this has been met with astounding success with the use of multiple kinase inhibitors like sorafenib and sunitinib.

Therefore, the emergence of targeted therapy has markedly improved the treatment outcome of both haematological and epithelial cancers. We look forward to further improvement with the emergence of new targeted therapies, or after optimisation of their use in different phases of treatment such as the role of maintenance therapy with targeted therapy, or their role in combination with chemotherapy or even with other targeted therapies. Therefore, the march is on!

References