Editorial

Blood cancers: Flowing the right way!

Starting from recognition and chemotherapeutic treatment of hematolymphoid malignancies, the science of blood diseases has seen major advances in recent years, especially identification of molecular pathways involved in pathogenesis and development of targeted therapies with high efficacy and limited toxicities even in relapsed/refractory diseases.

Chronic myeloid leukemia (CML) has been a prototype of success of targeted therapy. CML is uniformly associated with translocation between long arms of chromosome 9 and 22 (t9:22) (q32;q11) leading to the formation of Philadelphia chromosome and a chimeric fusion gene BCR-ABL and its abnormal protein product which is central to pathogenesis of CML. BCR-ABL has intrinsic tyrosine kinase activity and is an attractive target of tyrosine kinase inhibitors (TKIs).^[1] The World has seen the magic of TKIs in changing the picture of CML treatment and outcome. Similar success story has been witnessed in acute promyelocytic leukemia by drugs targeting PML-RARA fusion gene.^[2] There are many more drug targets being identified and explored in clinical trials.

Decade of 2000s saw a major change in the outcome of lymphoma patients with introduction of anti-CD20 antibody (rituximab) in frontline treatment of CD20 expressing B-cell malignancies. Similarly, monoclonal antibodies targeting CD22, CD30 has been found to be successful in salvaging multiple line treated and refractory patients with lymphomas expressing respective antigen.^[3]

Myeloma similarly, after success of newer proteasome inhibitors and antiangiogenic drugs, has seen many new drug targets such as HDAC, SLAMF7, and CD38. Vorinostat, elotuzumab, and daratumumab, respectively, target HDAC, SLAMF7, and CD38 and are effective in multiline treated myeloma.^[4]

Major pathogenic pathways or associated gene aberrations have been identified for most of the hematological malignancies and are being explored for being drug targets. A major breakthrough is the development of small molecule inhibitors of downstream of B-cell receptor (BCR) pathways. Ibrutinib (a Bruton's TKI) and idelalisib (a PI3K inhibitor as well as BCR signaling inhibitor) are promising new targeted therapies not only for relapsed refractory B-cell malignancies

but also in upfront settings in certain high-risk diseases such as chronic lymphocytic leukemia with del 17p.^[5]

A breakthrough in therapeutics is identification of the role of evasion of immune checkpoints by advancing malignancies by expression of programmed death ligand-1 (PDL-1) on the surface of tumor cells interacting with programmed death-1 (PD-1) molecule on activated lymphocytes. In trials, anti-PD-1 or anti-PDL-1 drugs have shown promising results even in advanced refractory Hodgkin lymphoma.^[6]

One of the major advances in field of hematology is evolution of cellular therapies over the past five decades, most popularly in the form of allogeneic stem cell transplantation (allo-SCT) from a treatment offered to terminally ill to now in the first line for many of high-risk malignancies and marrow failure syndromes. Despite availability of large voluntary donor pool/registries, nearly 30% of patients in need of transplant could not find a suitably matched donor. There is additional cost involved in procurement of matched unrelated donor stem cells or unrelated cord cells. Moreover, the time taken to procuring unrelated stem cells is also one of the major constraints for the patient in dire need of allo-SCT. Haploidentical donors are readily available in family for most of the patients but was not routinely offered to most of patients due to high treatment-related mortality and limited availability of *ex vivo* graft manipulation techniques. Haploidentical SCT has seen major paradigm shift from the use of sophisticated and expensive techniques of *ex vivo* graft manipulation to selective *in vivo* alloreactive T-cell depletion by cheaper high-dose posttransplant cyclophosphamide (PTCy).^[7] This way the survival posthaploidentical SCT is similar to matched donor allo-SCT with added advantage of better immune recovery and lesser opportunistic infections.^[8] Haploidentical SCT has already an established and popular modality of allo-SCT in most parts of the world after the success of PTCy-based regimes.

Future of hematology sees an era of molecularly defined entities, targeted therapies, and probably cellular therapies to provide antitumor immunity.^[9] Chimeric antigen receptor (CAR) directed engineered T-cells (CAR-T) have shown durable responses in patients with refractory hematological malignancies. CAR-T cells are long-lived cells and provide

long-lasting immunity against tumor. Both autologous and allogeneic CAR-T cells are in trial.

Current issue of Asian journal of clinical oncology is encompassing reviews on hematological malignancies with a focus of recent developments.

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Access this article online	
Website: www.asjo.in	Quick Response Code
DOI: 10.4103/2454-6798.180587	

How to cite this article: Agarwal N, Ahmed R, Bhurani D. Blood cancers: Flowing the right way!. *Asian J Oncol* 2016;2:1-2.