COMMENTS : TARGETED THERAPY FOR CML

Development of the organic compound, imatinib mesylate (chemically a 2 – phenylypyrimidine derivative) and its clinical efficacy that surpassed all expectations in Ph+ (bcr-abl+) CML has brought about a paradigm shift in management of the disease.\(^1\)\(^2\) In newly diagnosed CML-CP patients complete hematologic remission occurs in >95%, major cytogenetic response in 90% (complete in 84%) and major molecular response (3 log reduction of bcr-abl transcript levels) in 40% (IRIS study).\(^3\)

However, the response is usually inferior in late chronic phase who have been receiving Interferon alfa (IFN-\(\alpha\)) or chemotherapeutic drugs. A number of studies including (by Brijesh Arora et al) that appears in the current issue of this journal confirm this\(^4\). Another Indian study published recently also showed nearly similar results\(^5\). It appears that delay in instituting effective therapy allows clonal evolution and possibly mutations in the bcr-abl protein.

With the kind of positive attitude brought about by the drug among patients and physicians alike, most patients now prefer not to opt for allogeneic stem cell transplantation. It is hoped that the excellent response (cell kill) achieved by imatinib will remain substaned for years in most of the patients. At least 75% of patients continue to remain in the imatinib arm of the IRIS study after a median duration of 42 months and the overall survival is >85%\(^6\).

Currently, the focus is on the unravelling development of acquired resistance against imatinib even in chronic phase.\(^7\) The mechanism of resistance could be, 1) over expression of the bcr-abl protein. 2) mutations in the bcr-abl kinase domain.\(^8\) The number of mutations appears to be detected increasingly (>35 so far). How these mutations develop in the chimeric protein has not been studied in depth yet. Some of these mutations confer absolute resistance (e.g. T315) against imatinib, while some others do not seem to have significant impact.\(^9\) More Sinister could be emergence of clonal evaluation.\(^10\) This may herald rapid progression of the disease in many patients.
This had led the researchers to develop newer molecules like BMS 354825 and AMN 107 that are effective even in patients with bcr-abl mutations except those like T315. These molecules are now in phase I/II clinical trials. More such molecules will emerge in near feature.11

These are exciting days for the patients with CML and scientists involved in the field – newer drugs, newer technologies to detect (MRD) minimal residual disease levels and abilities to live a normal life without too many debilitating toxicities. Everyday seems to bring in a new hope and also some despair. There is a large pool of young CML patients in India (probably the most common leukemia among adults in India).12 Many large institutions have been treating these patients with imatinib that is available on compassionate basis through the Maxfoundation and Novartis (GIPAP). How I wished a collaboration among the physicians for compilation of the clinical data and development of central facilities for molecular work! It is so painful to see the opportunities pass by.

In this greatly hopeful scenario is the grim reminder of biology of the blastic phase CML and its temporary response to the targeted therapy, such outcome points to the need of better understanding of “two-hit” or “multi-hit” mechanism of development of malignancies and subsequent steps to develop targeted molecules. There appears to be an emergence of combination targeted therapy era, reminiscent of golden era of evolution of combination chemotherapy of 1970s and early 1980s.

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REFERENCES: