

## The Reshaping of Hematology Practice in the 21<sup>st</sup> Century

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In the emerging era of personalized medicine, the concept is changing from “one treatment fits all” to giving “the right treatment to the right person in the right dose and right time”. This also implies a better patient safety and quality of life, renewing the principle of “*first do no harm*”.

The explosion of biology information and the rapid advances in biotechnology are rapidly changing the current status of hematology practice. Innovative capabilities in genomics, proteomics and transcriptomes are reflected into vast developments in (diagnostics) and (therapeutics) e.g. increased diagnostic sensitivity, better risk stratification, disease monitoring, progressive use of chemo-free strategies, better disease control, improved life expectancy and better management of poor risk groups as ‘elderly’ patients and patients with comorbidity [1].

Recently, many new techniques of genomic analysis have been applied to hematology diagnosis including; antigen receptor gene rearrangements in lymphoid malignancies, molecular characterization of neoplasms with no recurrent cytogenetic abnormalities e.g. AML and quantitative molecular monitoring of leukemia and lymphoma with redefining disease remission. In addition, functional genomics as RNAi screening, array comparative genomic hybridization, and single nucleotide polymorphism arrays have identified novel molecular abnormalities. Epigenomics has also identified defects in transcriptional control and allowed the development of novel approaches to molecular diagnostics and therapeutics.

Pharmacotherapy and pharmacogenomics are other areas with rapid evolution e.g. tailor-made chemotherapeutics, monoclonal antibodies, epigenetic modifiers, newer immune-modulators, enzyme replacement therapy and many molecules which target numerous pathways in cell division, growth, proliferation, and apoptosis. In addition, growth factors, newer thrombin inhibitors, safer plasma-derived protein molecules and recombinant molecules, have wide applications in benign and neoplastic hematology. New biologic information has also allowed other applications of old molecules as for example the use of thalidomide as an anti-angiogenic molecule [2].

Consequently, drastic changes in hematology practice are evolving. Top on the list is hematological malignancy. Most notable examples are; NHL-CLL-MM Chemo-immunotherapy, new drugs; TK inhibitors (1st, 2nd, 3rd generation) in CML and Ph.+ ALL; APL therapy change from ATRA (1st example of targeted therapy) to chemo-free strategies; change in Hairy cell leukemia management (IFN, CDA, DCF) and change in ALL management in childhood, adolescents and young adults. The diagnosis and differential diagnosis of the rare pediatric myelodysplastic syndromes (MDS) and juvenile myelomonocytic leukemia (JMML) has been better clarified with the emergence of recent genetic insights that may be used for treatment stratification. In addition, there has been increased clinical use of monoclonal antibody (Moab) in many diseases with progressive personalization of treatment based on MRD monitoring (e.g. APL, ALL, CML, CLL, NHL, MM) [3].

CML is a prototype of a hematologic neoplasm with a drastically improved outcome since the introduction of Gleevec therapy, in which the average life expectancy almost reached that of the normal population.

Another worth mentioning disorder which is undergoing substantial practice changes in the genomic era is multiple myeloma (MM), which emerged from a uniformly fatal malignancy to one with more than a double increase in median survival and even a prospect of cure. This change is related to both more comprehensive cytogenetic, molecular and proteomic techniques with a better understanding of

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disease pathophysiology as well as to the rapid evolution of novel new therapies which increased antitumor response rates and which provide new options for patients with resistant disease. Examples include proteasome inhibitors, monoclonal antibodies and histone deacetylase inhibitors which are currently at various stages of drug approval by FDA and EMA. The Substantial improvement in techniques and methods for risk stratification, MRD detection and monitoring in MM including; multiparameter flow cytometry (MFC) and immunoglobulin (Ig) allele-specific oligonucleotide-based quantitative PCR (ASO-PCR) and next generation sequencing (NGS) of Ig genes, is deriving a changing paradigm of MM with; recent revision of practice guidelines, extended therapeutic options and improved outcome profile. Major areas of change in MM management include; therapeutic consideration for very high risk patients with smoldering myeloma (with a >80% risk of progression) [4]. Another important change is the introduction of post-transplantation consolidation and maintenance therapy with the aim of achieving a minimal residual disease negative state, potentially improving progression-free survival (PFS), and even overall survival (OS) [5]. A third major advance is the introduction of new agents; including thalidomide, lenalidomide, bortezomib, into standard care for many patients after ASCT. Furthermore, the development of proteasome inhibitors has allowed a therapeutic option for high-risk patients e.g. older patients and those with certain complications e.g. renal insufficiency [6].

At the core of the changing hematology practice is the increased interest in genetic predisposition of hematological neoplasms, both familial and sporadic. Phenotypic heterogeneity, incomplete penetrance, autosomal recessive inheritance, sporadic cases, and somatic mosaics may sometime obscure the underlying genetic syndrome. These may present as de novo AML and MDS in children and young adults. Suggested screening panels include mutations in the ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1, SRP72 genes in addition to recognition of possible hereditary BM failure syndromes. Detection of signature cytogenetic or molecular abnormality or diagnosis of an apparently de novo AML with dysplastic features in a young adult should alert for the possibility of an occult genetic predisposition syndrome [7].

Over 250 germ line mutations throughout the TP53 gene have been linked to familial cancer predisposition, together with a number of genetic modifiers both within the TP53 gene and in related genes e.g. SNP309 (T>G), rs2279744, MDM2. A classic familial cancer predisposition syndrome with evolving new criteria (Li-Fraumeni Syndrome-LFS) showed a definite

association with TP53. Similarly, a subtype of pediatric ALL with low hypodiploidy was recently linked with germ line TP53 mutations. Recently, the National Comprehensive Cancer Network (NCCN)' Current practice guidelines (2013), recommended yearly physical examinations, surveillance based on family history, and consideration of inclusion into novel screening clinical trial for all individuals with LFS. In addition, following telomere shortening as a clinical biomarker, and accumulation of copy number variations (CNVs) which reflect progressive genomic instability have been suggested for risk stratification in these patients. Multiplex genetic testing, including gene panels, and whole exome/genome sequencing will probably identify new genotype-phenotype relationships, expand current definitions, and initiate development of new clinical guidelines for identifying persons at risk in germ line TP53 mutations. For individuals of childbearing age in families with TP53 germ line mutations, reproductive genetic counseling should be offered with the possibility of pre-implantation genetic diagnosis.

Lastly, the rapid advancement in hematology practice with rapid bench to bedside translation will necessitate parallel development in many aspects including; advanced and accessible laboratories closely interacting with clinicians, access to new drugs, networking and collaboration between specialty centers both national and international, central handling and banking of biologic material, adequate funding, interaction with pharma, dedicated and motivated individuals and teams, and a role of physician-scientists.

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