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Introduction by the Guest Editor: At a cross road to Cure: From molecule to management strategies in multiple myeloma

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Multiple myeloma (MM) is a heterogeneous disease with variable genomic and molecular characteristics and diverse clinical outcomes including response to therapy and overall survival. With the advent of modern molecular methodologies, including high-throughput genomic and epigenomic profiling, significant advances have occurred both in our understanding of the disease biology, as well as correlates of response and resistance to therapy.

The initial risk-determination using clinical features such as immunoglobulin subtype and number of bone lesions has been replaced by genetic changes utilizing cytogenetics and fluorescent in situ hybridization (FISH). Even these genomic markers are now being supplanted by mutational analysis and changes in gene expression profile. For example, now patients with del17p along with mutation in p53, a biallelic inactivation of p53, is considered as carrying the highest risk of adverse outcome. Similarly, whole genome sequencing is providing a new insight into development and progression of plasma cell disorder from early stage disease to symptomatic multiple myeloma. A unique analysis of paired sample from patients at smoldering stage and then at progression to myeloma has revealed a set of patients who genomically are identical to symptomatic myeloma suggesting that progression may reflect increasing tumor burden leading to clinical impact which currently divides the 2 conditions; while a second group requires acquisition of new mutational change before progressing to myeloma.¹ Such analysis and their validation are likely to lead to both newer definition of early stage plasma cell disorder as well as development of preventative as well as novel therapeutic approaches.

These advances have allowed for identification of new targets and effective novel agents in myeloma.² Five new drugs have been approved for treatment in myeloma in the last five years, including 2 new antibodies. These advances along with extensive utilization of immunomodulatory agents and proteasome inhibitors have significantly improved, both frequency and extent of responses. Two drug regimens have been replaced by three and four drug combinations, which achieves close to a hundred percent responses including complete remissions in over half of all patients.³ Overall survival has increased from three years to close to a median of ten years, and patients have significant improvement in quality of life.⁴

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The recent emphasis now is to further improve the depth of the response paving the way for the evaluation of minimal residual disease as an important endpoint.

This significant improvement in our understanding of the disease biology translating into multiple therapeutic options has created an intricate problem for both academics as well as physicians in practice. The complexity of therapeutic algorithms has amplified with the number of three-drug combinations becoming the standard of care in relapsed myeloma within the backdrop of four-drug-regimens being utilized as an induction regimen. Number of currently ongoing clinical studies are investigating important questions in myeloma at different stages of the disease and recent studies have re-emphasized the importance of high-dose chemotherapy. The explosive developments in Immuno-oncology has also permeated into therapy of myeloma, with various immuno-therapeutic options including vaccination and CAR-T studies under intense investigation. This emerging data and knowledge requires its dissemination for its greater application and utilization in day-to-day practice to improve both patient outcome as well as quality of life.

This special issue of The Cancer Journal, the Journal of Principle and Practice of Oncology, is expected to fill some of the void in regard to understanding of these advances in myeloma with greater focus on therapeutic options and opportunities. The issue provides discussion on application and advances in targeting proteasome and use of immunomodulatory agents; developments of immunotherapeutic applications including incorporation of antibodies in therapeutic algorithm and various ongoing cellular therapies which have raised the possibility of achieving long-term disease control even in relapsed refractory disease.

The use of minimal residual disease, molecular subtyping, as well as mutational profiling is highlighted to help provide direction to physicians in appropriate utilization of various newer resources. Some of the newer developments with potential novel agents in pipeline are discussed and utilization of newer combinations with patient outcome in mind are also presented. I am confident that this issue of The Cancer Journal captures the essence and the depth of significant advances in myeloma and presents the data for its practical utilization today as well as with the hope of incorporation into future algorithm that is sure to lead to curative outcome.

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