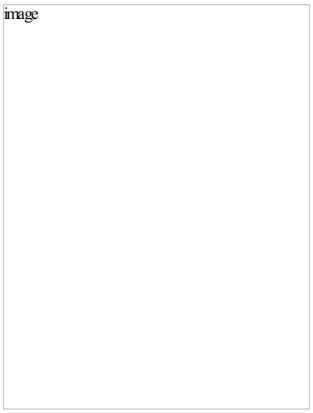

Minimal Residual Disease Detection by Flow Cytometry in Multiple Myeloma; Why and How?

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Minimal Residual Disease Detection by Flow Cytometry in Multiple Myeloma; Why and How?

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Abstract
The outlook for myeloma patients has steadily improved with the introduction of newer drug combinations in recent years. Unlike older therapies that largely achieved only modest levels of neoplastic clone reduction, the newer drug combinations have led to deeper suppression of myeloma clones in most patients. Frequently the neoplastic clones become undetectable with traditional disease evaluation approaches. Recent studies using ultrasensitive disease monitoring have demonstrated that patients with disease undetectable by traditional techniques show wide heterogeneity in disease levels varying by several orders of magnitude. Moreover, measurement of the depth of disease suppression even at very low level has emerged as the most powerful prognostication tool in myeloma. Minimal (or measurable) residual disease (MRD) evaluation has also been proposed as a relevant tool in assessment of drug efficacy and in selection of further therapeutic options. In the face of the robust MRD measurement utility data, it has become critical to develop widely applicable disease monitoring techniques that can be applied to more patients in a variety of clinical setting. Both DNA-based and flow cytometry-based approaches have been successfully developed for this purpose achieving sensitivity approaching 1 neoplastic cell in a million. This review article focuses on the theoretical and practical aspects and challenges of deep MRD monitoring in myeloma by flow cytometry. Challenges of flow cytometric disease monitoring in the era of antigen-directed therapy are also discussed.

Evolving treatment for multiple myeloma results in deeper responses requiring more sensitive assays

Until very recently multiple myeloma was considered an incurable disease with conventional therapeutic approaches. The assumption is based on the near uniform relapse of patients post treatment with older therapies [1, 2]. Relapses are almost certainly due to the residual neoplastic clones that constitute a reservoir of therapy-resistant disease. In the past, with less effective therapies the residual neoplastic cells could be readily demonstrated, even by relatively insensitive residual disease detection techniques such as fluorescence in-situ hybridization, immunohistochemical studies, and 4-color flow cytometric approaches with detection limits ranging from 0.01% to 5% [3-6].

Recent years have seen an explosion in availability of novel therapeutic options for treatment of the disease[2]. The advances in therapy are reviewed elsewhere in the issue. These newer therapies have resulted in longer progression free and overall survival improving the outlook of myeloma patients [2, 7, 8]. The improvements were also seen outside specific clinical trials. For instance, Fonesca et al. have shown a steady increase in overall survival in myeloma patients paralleling introduction of new therapies. Patients diagnosed in 2012 are 1.25 times more likely to survive the first two years compared to those diagnosed in 2006 according to US administrative claims [9].

Many patients are achieving durable remissions with newer therapies with residual neoplastic clones becoming undetectable by older methodologies. Fewer but nonetheless significant number of