XIII CONGRESSO NAZIONALE SIES 2014
RIMINI, 15-17 OTTOBRE

Abstract N. 0073

Argomento: 15. Monoclonal Gammopathies & Multiple Myeloma

ANALISI DEL NUMERO DI COPIE E SEQUENZA DEL DNA IN CAMPIONI SEQUENZIALI DI MIELOMA ALLA DIAGNOSI E RECIDIVA

DNA COPY NUMBER AND WHOLE-EXOME SEQUENCING ANALYSES IN SEQUENTIAL MYELOMA SAMPLES AT DIAGNOSIS AND RELAPSE

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Introduction. Multiple myeloma (MM) is a plasma cell (PC) malignancy characterized by a marked genetic heterogeneity at onset, followed by further genomic complexity acquired during disease progression and particularly after treatment. To gain insight into the molecular evolution associated with MM progression, we investigated sequential samples of 7 MMs and 1 primary PC leukemia (pPCL) by genome-wide DNA copy number analysis and whole-exome sequencing (WES).

Methods. Highly purified PC samples obtained at diagnosis and relapse after first line therapy (7 symptomatic MMs and 1 pPCL) were subjected to genome-wide DNA profiling (all cases) and WES (1 MM and 1 pPCL samples, with matched negative controls). Copy number data were generated on Affymetrix CytoScan HD Array, using the Chromosome Analysis Suite software. Single sample analysis was performed with default parameters and setting the Reference Model. WES was carried out on Illumina GAIIx platform and variant calling was performed using Mutect algorithm, by separately comparing primary and progression samples to its matched normal control.

Results. Concerning regions of prognostic importance, 1p loss was identified as a novel lesion or evolving from a sub-clone in 3 relapsed samples, whereas 1q gain or 17p loss were respectively acquired in two cases. Notably, some alterations, present at diagnosis only in sub-clones, were detected in the majority of tumor cells in at least one of 5 relapsed MMs. Such lesions involved single or combined gains or losses of whole chromosomes (chr) 3, 8, 9, 18, 20, aberrations of short/long arms of chrs 11, 13, 14, 15, 18, 21 or smaller altered regions on chrs 4, 10, 12, 16, 17, 19. Interestingly, deletions involving chr 5q (3/8 relapsed MMs) or 8q (2/8 relapsed MMs) were detected as de novo acquired lesions. Furthermore, we investigated by WES two cases, a MM progressed to secondary PCL (sPCL) and a pPCL patient at diagnosis and relapse. Each patient showed a dynamic mutational pattern, involving both the acquisition and the loss of a large number of point mutations. Specifically, 19 genes were exclusively mutated in MM at diagnosis and 66 only in sPCL phase, whereas 12 genes were mutated in both conditions; in pPCL patient, 138 genes were evidenced at diagnosis and 166 at relapse, while 78 were commonly altered. Genes acquiring mutations in disease course were mostly involved in DNA repair, histone methylation, protein metabolism, regulation of NF-kB cascade, focal adhesion and MAPK signaling pathways. Concerning genes frequently altered in MM, it is worth reporting mutations of TP53 and CYLD at relapse, in sPCL and pPCL, respectively.

Conclusions. Our data highlight the importance of using high-throughput approaches to provide insights into the definition of genetic alterations potentially related to mechanisms of drug resistance and MM progression.

Presentazione: Orale *Pubblicabile:* SI