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Autore	Ferrari, Anna
Titolo	Depicting the role of CDKN2A/ARF alterations in adult BCR-ABL1-positive acute lymphoblastic leukemia patients: from genomic deletions to prognostic impact [Tesi di dottorato]
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Sommario	This 9p21 locus, encode for important proteins involved in cell cycle regulation and apoptosis containing the p16/CDKN2A (cyclin-dependent kinase inhibitor 2a) tumor suppressor gene and two other related genes, p14/ARF and p15/CDKN2B. This locus, is a major target of inactivation in the pathogenesis of a number of human tumors, both solid and haematologic, and is a frequent site of loss or deletion also in acute lymphoblastic leukemia (ALL) ranging from 18% to 45% 1. In order to explore, at high resolution, the frequency and size of alterations affecting this locus in adult BCR-ABL1-positive ALL and to investigate their prognostic value, 112 patients (101 de novo and 11 relapse cases) were analyzed by genome-wide single nucleotide polymorphisms arrays and gene candidate deep exon sequencing. Paired diagnosis-relapse samples were further available and analyzed for 19 (19%) cases. CDKN2A/ARF and CDKN2B genomic alterations were identified in 29% and 25% of newly diagnosed patients, respectively. Deletions were monoallelic in 72% of cases and in 43% the minimal overlapping region of the lost area spanned only the CDKN2A/2B gene locus. The analysis at the time of relapse showed an almost significant increase in the detection rate of CDKN2A/ARF loss (47%) compared to diagnosis (p = 0.06). Point mutations within the 9p21 locus were found at very low level with only a non-synonymous substition in the exon 2 of CDKN2A. Finally,

	correlation with clinical outcome showed that deletions of CDKN2A/B are significantly associated with poor outcome in terms of overall survival (p = 0.0206), disease free-survival (p = 0.0010) and cumulative incidence of relapse (p = 0.0014). The inactivation of 9p21 locus by genomic deletions is a frequent event in BCR-ABL1-positive ALL. Deletions are frequently acquired at the leukemia progression and work as a poor prognostic marker.
Localizzazioni e accesso	http://memoria.depositolegale.it/*/http://amsdottorato.unibo.it/3617/1/Ferrari_Anna_Tesi.pdf