The ABCB1 pharmacogenetics of R-CHOP regimen in mantle cell lymphoma patients: a substudy from the FIL MCL-0208 trial

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The prediction of treatment efficacy is a growing field of pharmacology, especially for haematological malignancies that have a poor prognosis. Several clinical trials are investigating the relationships between antineoplastic drug pharmacodynamics and pharmacogenetic factors (i.e., gene polymorphisms). The mdr1 gene encodes the transmembrane transporter ABCB1 that plays a pivotal role in predicting drug efficacy. Indeed, the mdr1 gene harbours several single nucleotide polymorphisms (SNPs) affecting susbstrate affinity and transporter activity. The c.1236C>T, c.2677G>T/A and c.3435C>T SNPs have been investigated as single polymorphisms or in haplotypes. Many drugs are known substrates of ABCB1, including doxorubicin, vincristine [1] and, in a lesser degree, prednisone [2]. Interestingly, these drugs are combined with cyclophosphamide and rituximab within the R-CHOP schedule for the treatment of lymphomas. Therefore, the present study was aimed at investigating every relationship between ABCB1 SNPs and efficacy of R-CHOP in mantle cell lymphoma patients.

Genomic DNA was obtained from 291 younger patients (78.3% of men and 21.7% of women, age: 558 years) affected by mantle cell lymphoma. All patients were enrolled in the prospective MCL0208 clinical trial, sponsored by the Fondazione Italiana Linfomi (FIL) and gave their informed consent to trial participation and planned analyses. Clinical data from this phase III trial (NCT02354313) were derived from the second interim analysis. Patients' genotypes for c.1236C>T, c.2677G>T/A and c.3435C>T SNPs were obtained through allele-specific probes on an ABI-Prism 7900HT instrument (Thermo Fisher, Milan). Minor allele frequencies (MAFs) were obtained and the Hardy-Weinberg equilibrium (HWE) was checked. Genotypes were used to infer individual haplotypes by means of the Arlequin software. Finally, the progression-free survival (PFS), defined as the survival from enrolment up to progression or death, was adopted as a clinical endpoint of efficacy. The median follow-up for the enrolled patients was 36 months. Patients were grouped according to their genotypes or haplotypes and survival analysis was done. The level of significance was set at p=0.05.

The MAF values of the investigated SNP were very similar to those already published for the three SNPs (c.1236C>T, c.2677G>T/A and c.3435C>T, 0.433, 0.418 [0.383 T allele, 0.034 A allele] and 0.478, respectively) and the HWE was confirmed. The 3 loci were in strong linkage disequilibrium (r-square>0.460 and D' values >0.7 for all possible couples of SNPs) and 11 possible haplotypes were inferred. In particular, 21.0% of patients were homozygous for the wild type alleles (CGC/CGC), whereas 49.5% of patients were heterozygous (i.e., CGC/TTT, CGC/CTT, etc.). Finally, 29.5% of patients carried polymorphic alleles on both chromosomes (i.e., CGT/CGT). Survival analysis did not find any significant difference in PFS when patients were grouped on the basis of SNP genotypes. Similar findings were obtained when individuals were stratified according to mdr1

haplotypes, as described above (p=0.558). Only a modest trend (p=0.121) toward a worse PFS was identified in c.2677GG patients with respect to patients carrying at least 1 polymorphic T or A allele.

Despite the large number of patients evaluated and the homogeneous treatment received, mdr1 polymorphisms seem not able to predict the efficacy of R-CHOP in mantle cell lymphoma patients. it is conceivable that expanding the number of investigated genes/polymorphisms could led to the identification of predictive markers of efficacy.

References

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