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Title: Germline genetic polymorphisms influence chemotherapy toxicity and disease outcome in osteosarcoma.

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Aims: Osteosarcoma is the most common malignant bone tumour in children and young people. Approximately 40% patients respond poorly to highly toxic pre-operative MAP (**M**ethotrexate, **A**driamycin, **C**isplatin) chemotherapy with consequent inferior survival. The role of single nucleotide polymorphisms (SNP) in drug response and toxicity is reported in acute leukaemia and some solid tumours. This study aimed to investigate the influence of drug target and metabolising gene polymorphisms on tumour response, survival and chemotherapy toxicity in osteosarcoma.

Methods: Sixty patients treated in the London Sarcoma Service between 2001 and 2008 were enrolled in this retrospective study. Eligible patients were aged >16 years who had completed MAP chemotherapy for osteosarcoma. CTCAE grades for chemotherapy-induced toxicities were obtained from patient records. Tumour histological response was graded as good (>90% necrosis) or poor (< 90% necrosis) in surgical resection specimen. Genomic DNA was extracted from venous blood samples taken after completion of chemotherapy and all patients manually genotyped for 5 polymorphisms. Genome-wide SNP analysis was performed on 50 patients using the Illumina 610 Quad array and genotypes assigned using BeadStudio software. For initial analysis, 35 candidate functional polymorphisms from 20 genes within MAP drug pathways were selected on the basis of previously described associations or putative functional effects.

Results: Poor histological response was significantly associated with SNPs in the ATP-binding cassette (ABC) drug efflux transporter ABCC2 c.24C>T (rs717620) (OR 21 95% CI 1.6-273, p=0.02), and the detoxification enzyme Glutathione S-transferase (GST) P1 c.313A>G p.Ile^{105}Val (OR 7.8, 95% CI 1.6-37.5, p=0.01). Progression-free survival (PFS) was negatively influenced by SNPs in the folate pathway (RFC c.80G>A p.Arg^{27}His p=0.02) and cell cycle regulation (CCND1 c.870A>G p.Pro^{241}Pro p=0.012). GST enzymes implicated in detoxification of cisplatin and doxorubicin, also decreased PFS (GSTP1 c.313A>G p.Ile^{105}Val p=0.025, GSTT1 null allele p=0.006). Toxicity of **AP** chemotherapy was enhanced both by Nucleotide Excision Repair pathway (ERCC1 c.354T>C p.Asn^{118}Asn, c.1510C>A p.Gln^{504}Lys) and detoxifying GST (GSTP1 c.313A>G p.Ile^{105}Val) SNPs. The latter also increased the risk of anthracycline cardiotoxicity. Severe **M** toxicity was associated with folate pathway (MTHFR c.1298A>C p.Glu^{429}Ala, MTHFD1 c.1958G>A p.Arg^{653}Gln) and ABC SNPs (ABCB1 c.3435T>C Ile^{145}Ile, ABCC2 c.3563T>A p.Val^{1188}Glu). The risk of nephrotoxicity was increased by SNPs in ERCC2 (c.2251A>C p.Lys^{751}Gln) and MTHFR (c.677C>T p.Ala^{222}Val), key genes in cisplatin and methotrexate pathways respectively.

Conclusions: This study represents the most comprehensive investigation of the role of genetic polymorphisms on chemotherapy toxicity and outcome in osteosarcoma. Using a pathway-based approach, our findings suggest pharmacogenomic profiling may facilitate optimisation of current chemotherapeutic strategies and prediction of severe toxicity. A larger prospective study is warranted.