Testicular cancer is one of the most commonly occurring malignant tumors in young men with fourfold higher rate of incidence and threefold higher mortality rates in Chile than the average global rates. Surgery is the initial line of treatment for testicular cancers, and is generally followed by chemotherapy, usually with combinations of bleomycin, etoposide, and cisplatin (BEP). However, the adverse effects of chemotherapy vary significantly among individuals; therefore, the present study explored the association of functionally significant allelic variations in genes related to the pharmacokinetics/pharmacodynamics of BEP and DNA repair enzymes with chemotherapy-induced toxicity in BEP-treated testicular cancer patients. We prospectively recruited 119 patients diagnosed with testicular cancer from 2010 to 2017. Genetic polymorphisms were analyzed using PCR and/or
qPCR with TaqMan® probes. Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events, v4.03. After univariate analyses to define more relevant genetic variants (p < 0.2) and clinical conditions in relation to severe (III-IV) adverse drug reactions (ADRs), stepwise forward multivariate logistic regression analyses were performed. As expected, the main severe ADRs associated with the non-genetic variables were hematological (neutropenia and leukopenia).

Univariate statistical analyses revealed that patients with ERCC2 rs13181 T/G and/or CYP3A4 rs2740574 A/G genotypes are more likely to develop alopecia; patients with ERCC2 rs238406 C/C genotype may develop leukopenia, and patients with GSTT1-null genotype could develop lymphocytopenia (III-IV). Patients with ERCC2 rs1799793 A/A were at risk of developing severe anemia. The BLMH rs1050565 G/G genotype was found to be associated with pain, and the GSTP1 G/G genotype was linked infection (p < 0.05). Multivariate analysis showed an association between specific ERCC1/2 genotypes and cumulative dose of BEP drugs with the appearance of severe leukopenia and/or febrile neutropenia. Grades III-IV vomiting, nausea, and alopecia could be partly explained by the presence of specific ERCC1/2, MDR1, GSTP1, and BLMH genotypes (p < 0.05). Hence, we provide evidence for the usefulness of pharmacogenetics as a tool for predicting severe ADRs in testicular cancer patients treated with BEP chemotherapy.