Hepatocellular carcinoma (HCC) is the most common primary liver tumor worldwide. Current medical therapy for HCC has limited efficacy. The present study tests the hypothesis that human cerebral endothelial cell-derived exosomes carrying elevated miR-214 (hCEC-Exo-214) can amplify the efficacy of anti-cancer drugs on HCC cells. Treatment of HepG2 and Hep3B cells with hCEC-Exo-214 in combination with anti-cancer agents, oxaliplatin or sorafenib, significantly reduced cancer cell viability and invasion compared with monotherapy with either drug. Additionally, the therapeutic effect of the combination therapy was detected in primary tumor cells derived from patients with HCC. The ability of hCEC-Exo-214 in sensitizing HCC cells to anti-cancer drugs was specific, in that combination therapy did not affect the viability and invasion of human liver epithelial cells and non-cancer primary cells. Furthermore, compared to monotherapy with oxaliplatin and sorafenib, hCEC-Exo-214 in combination with either drug substantially reduced protein levels of P-glycoprotein (P-gp) and splicing factor 3B subunit 3 (SF3B3) in HCC cells. P-gp and SF3B3 are among miR-214 target genes and are known to mediate drug resistance and cancer cell proliferation, respectively. In conclusion, the present *in vitro* study provides evidence that hCEC-Exo-214 significantly enhances the anti-tumor efficacy of oxaliplatin and sorafenib on HCC cells.