J Clin Exp Pathol 2018, Volume 8
DOI: 10.4172/2161-0681-C3-052

Unraveling intricate molecular interactions of drug resistance pathways in neoadjuvant chemotherapy of TNBC patients: Exploring the design of individualized treatment strategies

Fouzia Guestini[1], Keely May McNamara[1], Hironobu Sasano[1], Katsuhiko Ono[1], Minoru Miyashita[1], Takanori Ishida[1], Noriaki Ohuchi[1], Saki Nakagawa[1], Hisashi Hirakawa[2], Kentaro Tamaki[3], Yasuyo Oi[4], Yoshiaki Rai[4] and **Yoshiaki Sagara[4]**

[1]Tohoku University, Japan
[2]Kosai Hospital, Japan
[3]Nahanishi Clinic, Japan
[4]Sagara Hospital, Japan

Neoadjuvant (NAC) and adjuvant chemotherapies are effective at least in the early clinical course of triple-negative breast cancer (TNBC) patients but most eventually chemoresistance occur. Therefore, in this study, we assessed the panel of KI67, TopoIIα, Bcl2, p53, PTEN, vimentin, ABCC1/MRP1, ABCB1/MDR1, ABCG1/BCRP1, β-catenin, all reported to be involved in drug resistance and tumor progression, in surgical pathology specimens before and after NAC in 148 cases of Japanese TNBC patients using immunohistochemistry, in order to explore the potential mechanisms of chemoresistance in these patients. TNBC patients harboring a low proliferative KI67 labeling index tended to be less likely to respond to the neoadjuvant treatment Anthracycline-Taxanes-based (pathologic complete response: p=0.009), but there were no significant differences of eventual clinical outcome of these patients after the treatment (Overall Survival: p=0.07). Drug efflux pumps (ABCC1/MRP1 and ABCB1/MDR1) have been reported to play a pivotal role in the development of therapeutic resistance and, in our present study the profiles of those above did predict neoadjuvant treatment response (pathologic complete response-ABCC1/MRP1: p=0.057; clinical treatment response-ABCG1/BCRP1: p=0.017), and the up-regulation of the above mentioned multidrug resistance proteins after treatment also did predict local (Disease Free Survival: p=0.055; p=0.03) and distant relapse (p=0.0.36; p=0.037) in the univariate analysis and, the down-regulation of the tumor suppressor PTEN was significantly associated with relapse (p=0.038). We also assessed the correlation among these factors and significant correlations were observed among ATP-binding cassette proteins (ABCG2/BCRP1 with ABCC1/MRP1 p=0.001, p=0.013; and ABCB1/MDR1 p<0.0001, p=0.024), and with Bcl2 (ABCG2/BCRP1 p=0.027; ABCC1/MRP1 p<0.0001; p=0.006), vimentin (ABCC1/MRP1 p=0.065, p=0.046), and β-catenin (ABCG2/BCRP1 p<0.001, p=0.029; ABCC1/MRP1 p<0.0001, p=0.006) in the biopsy or surgery specimens respectively, as well as between vimentin and β-catenin (p=0.004) or Bcl2 (p=0.007) in the surgery specimens. These immunohistochemical results above all indicated the presence of "stemness" phenotype in these carcinoma cells in the primary tumors, which persisted following NAC. Of particular interest, the status of TopoIIα was significantly positively correlated with that of ABCG2/BCRP1 (p<0.0001, p=0.006) and β-catenin (p=0.001, p=0.005) in both biopsy and surgery specimens of NAC and with PTEN (p=0.003) in the surgical specimens. These results above did highlight the intricate relationship among the putative mechanisms such as epithelial-mesenchymal transition, wnt/β-catenin pathway, apoptosis and drug-efflux in the process of development of chemoresistance in TNBC patients. In summary, we studied the potential cellular mechanisms related to the regulation of the tumor cell proliferation and cellular availability of chemotherapeutic agents, involved in developing chemoresistance and relapse in NAC-treated TNBC patients. In addition, the "stemness" phenotype in the residual tumor cells of these patients following NAC could be responsible for chemoresistance and recurrence as well, leading to those cellular features as the potential targets in overcoming therapeutic resistance in these patients. The results above also indicated that not a single but multiple markers assessment should be incorporated to achieve the best therapeutic outcome in TNBC patients.

guestini.fouzia@gmail.com