Tailoring treatment for triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy

（書式１２）

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学位論文題目	Tailoring treatment for triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy (ネオアジュバント化学療法後の残存疾患を有するトリプルネガティブ乳癌患者のための治療選択)
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論文内容要旨

Purpose:

Triple-negative breast cancer (TNBC) patients with residual disease, following neoadjuvant chemotherapy (NAC) harbor higher risk of relapse, and eventual demise compared to those who achieve pathologic complete response. Therefore, the purpose of the present study was to characterize the molecular and pathway signatures of TNBC NAC-treated based on protein expression analyses and understand the underlying mechanisms of regulation leading to drug resistance.

Methods:

I studied 148 TNBC Japanese patients treated with anthracyclines/taxanes-based NAC. Ki67, Topoisomerase IIα (TopoIIα), PTEN, p53, Bcl2, vimentin, ABCG2/BCRP1, ABCB1/MDR1 and ABCC1/MRP1, β-catenin, FOXP3, CD8, were all immunolocalized in archival materials of the same patients before and after NAC. Tumor infiltrating lymphocytes (TILs) were first assessed in the Hematoxylin & Eosin slides. In the *in vitro* study the multidrug resistance proteins (ABCB1/MDR1, ABCG2/BCRP1, ABCC1/MRP1) messenger RNA (mRNA) expression was evaluated by real-time polymerase chain reaction under different

concentrations of chemotherapeutic agents in the mesenchymal stem-like TNBC cell line MDA-MB-231. The chemosensitivity of this cell line to Epirubicin, wnt3a and Akt inhibitor (MK2206) was determined using wst-8 colorimetric assay. PTEN RNA interfering was also used in order to knockdown PTEN expression in the cell line.

Results:

The status of vimentin, ABCG2/BCRP1, and increasing labeling index (LI) of TopoIIα and Ki67 and tumor infiltrating lymphocytes in biopsy specimens were significantly associated with those who responded to NAC treatment. The relative abundance of p53 ($p=0.003$), ABCC1/MRP1 ($p=0.033$), ABCB1/MDR1 ($p=0.022$) and a loss of PTEN ($p<0.0001$) in surgery specimens following treatment were associated with metastasis in lymph nodes, disease free survival or lymphovascular invasion. TopoIIα and PTEN status predicted overall survival in the biopsies and ABCC1/MRP1 predicted disease free survival. In addition, the status of PTEN, ABCC1/MRP1, ABCB1/MDR1, Bcl2 and vimentin in surgical specimens was also significantly associated with adverse clinicopathological factors, suggesting that these alterations could be responsible for tumor relapse in TNBC patients. The results of *in vitro* study indicated that ABCB1/MDR1 could play possible roles in the development of Epirubicin resistance in TNBC cell line, and that the resistance could be overcome by some multidrug resistance-reversing agents including wnt pathway and PI3K/Akt pathways inhibitors.

Conclusion:

Vimentin, Ki67, TopoIIα, PTEN, ABCC1/MRP1 and TILs status could predict treatment response and/or eventual clinical outcomes of TNBC patients NAC-treated. These results could also provide a thought provoking insight into the mechanisms of drug resistance and relapse of TNBC patients receiving NAC and offer a more individualized treatment option to overcome this resistance but further investigations are required for clarification.

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審　査　結　果　の　要　旨

博士論文題目　Tailoring treatment for triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy （ネオアジュバント化学療法後の残存疾患を有するトリプルネガティブ乳癌患者のための治療の調整）

所属専攻・分野名　医科学専攻　・　病理診断学　分野

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乳癌は本邦でもその頻度増加し女性にとって尤も発生頻度が高い悪性腫瘍の一つとなっている。　近年乳癌の中でもTNBC（triple negative breast carcinoma）とも呼ばれるサブタイプはER, PR、HER2などの特異的治療法が開発されておらず 他の乳癌サブタイプよりもその臨床予後は有意に悪い。一方この TNBC 患者では術前化学療法(NAC ： neoadjuvant chemotherapy) が広く実施され治療成績の向上に貢献している。 しかしこのNACは副作用も見られ全ての患者で効果がある訳ではない。 そこでこの NAC に対する治療効果あるいは抵抗性を示すバイオマーカーの開発が待たれてきた。

そこで今回のFouzia Guestiniの研究はVimentin, Ki67, TopoIIα, PTEN, ABCC1/MRP1 などの腫瘍細胞関連因子に加えて腫瘍組織内リンパ球の動態が NAC の治療効果ばかりでなくNACと同じ術後治療後の患者の臨床予後も示す事が出来ると言う極めて独創性が高く優れた研究成果である。このFouzia Guestiniの研究成果は今後の更なる発展が期待される優れた研究成果であるとも考えられる。

よって，本論文は博士（医学）の学位論文として合格と認める。