The epigenetic profile of triple-negative breast cancer (TNBC) showed a wide prevalence of MGMT promoter methylation. A aberrant methylation of MGMT seems to be an independent predictor of poor survival in patients with basal-like breast cancer.

Patients with MGMT-negative basal-like tumors who received cyclophosphamide had a significantly improved disease-free (DFS) survival compared with patients with MGMT-positive tumors.

Platinum-based drugs act as alkylating agents.

Even if the impact of MGMT promoter methylation in patients treated with alkylating agents, its role in patients receiving carboplatin is not clear.

We aimed to investigate the impact of MGMT methylation on pathological complete response (pCR).

We retrospectively evaluated 174 TNBC patients enrolled into the neo-adjuvant GeparSixto® trial from August 2011 to December 2012.

Patients were randomized to receive 18 weeks of neo-adjuvant treatment with paclitaxel (80mg/m²/week) and non-pegylated liposomal doxorubicin (20mg/m²/week) with or without addition of carboplatin (AUC 2.0-1.5/weeks).

Hormone-receptor status, HER2 status, and Ki67 were centrally confirmed prior to randomization.

We defined pCR as absence of invasive cancer in breast and lymph node (ypT0/is ypN0).

Bisulphite conversion of isolated DNA was performed using the EZ DNA Methylation Kit (Zymo Research). DNA was amplified using the PyroMark Q24 MasterMix (Qiagen) and methylation status was then determined by pyrosequencing.

Overall, 5 out of 98 CpG islands were examined.

If no CpG island is out 5 shows a methylation in ≥10%, the tumor was considered as methylated.

If a methylation rate of 5-10% was detected at minimum one CpG island, the tumor is considered as borderline.

All other samples are negative.

In this study no statistically significant association between MGMT methylation and pCR was found. Patients with MGMT methylation seemed to have a lower possibility to achieve a pCR and the addition of carboplatin seemed to reverse this effect. However, a clear classification of the borderline MGMT samples and further studies in larger series of TNBC are warranted.

**Background & aim**

**Materials and methods**

**Results**

Out of the 315 TNBC patients enrolled in the GeparSixto trial, a total of 210 tumors from the TNBC cohort were available with a tumor content >20%. In 174 tumors the methylation assay was performed successfully.

The number of tumors with methylated MGMT was similar in non-carboplatin versus carboplatin treated cohorts (figure 1):

- in the non-carboplatin group 20.9% (18 out of 86) of TNBC samples were methylated, 62.8% (54 out of 86) of TNBC samples were unmethylated, and 16.3% (14 out of 86) of TNBC samples were borderline.

- in the carboplatin group 19.3% (17 out of 88) of TNBC samples were methylated, 65.9% (58 out of 88) of TNBC samples were unmethylated, and 14.8% (13 out of 88) of TNBC samples were borderline.

In the entire TNBC cohort, there was no association between MGMT methylation status and pCR (p=0.522). However, a trend for a lower pCR rate was observed in TNBC patients with MGMT methylation who did not receive carboplatin (figure 2, A and B):

- in the non-carboplatin group: 33.3% (6 out of 18) of patients with methylated MGMT achieved pCR versus 51.9% (28 out of 54) of unmethylated and 21.4% (5 out of 14) of borderline (p=0.079).

- in the carboplatin group: 52.9% (9 out of 17) of patients with methylated MGMT achieved pCR versus 55.3% (26 out of 58) of unmethylated and 76.9% (10 out of 13) of borderline (p=0.320).

In TNBC patients with methylated MGMT, the addition of carboplatin resulted in a 20% increased pCR rate (p=0.241).

**Conclusions**

**References**

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