Predictive value of O6-methylguanine-DNA methyltransferase (MGMT) promoter gene methylation in triple-negative breast cancer patients receiving carboplatin

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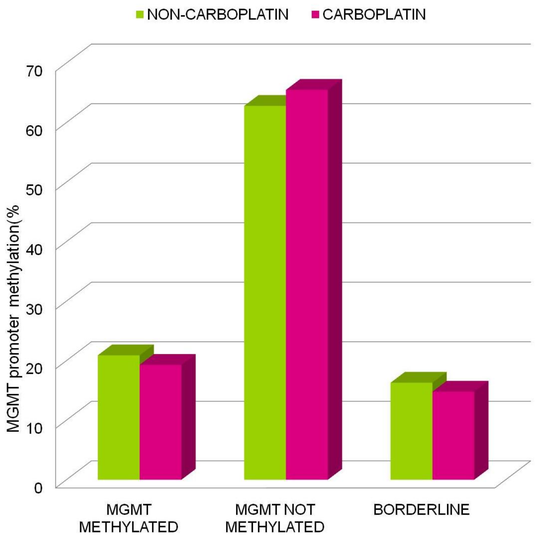
Background & aim

- The epigenetic profile of triple-negative breast cancer (TNBC) showed a wide prevalence of MGMT promoter methylation[1].
- Aberrant methylation of MGMT seems to be an independent predictor of poor survival in patients with basal-like breast cancer[2].
- Patients with MGMT-negative basal-like tumors who received cyclophosphamide had a significantly improved disease-free (DFS) and overall survival (OS) compared with MGMT-positive tumors[3].
- Platinum-based drugs act as alkylating-like agents[4].
- 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).

Materials and methods

- We retrospectively evaluated 174 TNBC tumors of patients enrolled into the neoadjuvant GeparSixto[5] trial from August 2011 to December 2012.
- Patients were randomized to receive 18 weeks of neoadjuvant treatment with paclitaxel (80mg/m^2/week) and non-pegylated liposomal doxorubicin (20mg/m^2/week) with or without addition of carboplatin (AUC 2.0-1.5/week).
- 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).
- Bisulfite 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 ≥1 CpG island out 5 shows a methylation in ≥10%, the tumor was considered as methylated.
  - If a methylation rate of 5-10% was detected in at minimum one CpG island, the tumor is considered as borderline.
  - All other samples are negative.

Figure 1: prevalence of MGMT promoter methylation in the GeparSixto TNBC cohort, according to study treatment arm

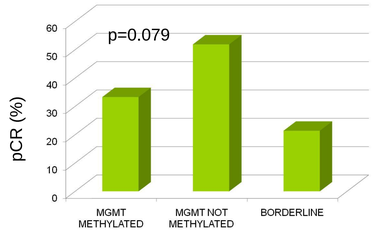


Results

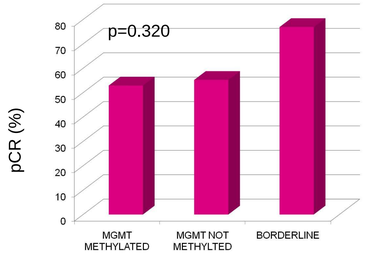
- Out of the 315 TNBC patients enrolled in the GeparSixto trial, a total of 210 tumors from the TNBC cohort were available with a tumor content >20%. In 174 tumors the methylation assay was performed successfully.
- The number of tumors with methylated MGMT was similar in non-carboplatin versus carboplatin 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, 65.5% (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 received 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% (3 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 55.2% (32 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).

Figure 2: pCR rate according to MGMT promoter methylation status in the GeparSixto TNBC cohort

A: non-carboplatin group



B: carboplatin group



Conclusions

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.

References

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