Fecal microbiota composition is related to response to CDK4/6-inhibitors in metastatic breast cancer: a prospective cross-sectional exploratory study

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Background:

CDK4/6-inhibitors with endocrine therapy represent the standard of treatment of hormone receptor-positive/HER2-negative metastatic breast cancer (MBC). Gut microbiota seems to predict treatment response in several tumor types, being directly implied in chemotherapy resistance and development of adverse effects. No evidence is available on gut microbiota impact in efficacy of breast cancer treatment.

Material and Methods:

We assessed the potential association among fecal microbiota and therapeutic efficacy of first-line CDK4/6-inhibitors on 14 MBC patients classified as responders (R) and non-responders (NR) accordingly to time of relapse. A stool sample was collected at baseline and DNA was extracted and sequenced to assess its bacterial composition. Associations with R and NR were studied.

Results:

Globally, no significant compositional differences were observed among R and NR in terms of α- and β-diversity. At the phylum level a slightly significant difference was observed between NR and R ($p<0.001$), with *Euryarcheota* and *Bacteroidota* being more prevalent in NR and *Actinobacteriota* more abundant in R. One-hundred-thirty-one bacterial species were identified. *Clostridium innocuum* and *Schaalia odontolytica* ($p=0.031$ both) were exclusively present in NR; *Bifidobacterium longum* ($p=0.014$) and *Ruminococcus callidus* ($p=0.020$), were significantly associated to R. Network analysis evidenced two major clusters of bacterial species with differential relative abundance between R and NR ($p<0.001$).

Conclusions:

Stool microbiota might be able to early-predict responses to CDK4/6-inhibitors and endocrine therapy. Ablation of a specific gut microbiota by targeted antibiotic therapy or fecal microbiota transplantation or oral administration of probiotics with *Bifidobacteria* can be hypothesized to improve response to CDK4/6-inhibitors. These results reveal that the commensal gut microbiota contributes to endocrine sensitivity and/or resistance in metastatic breast cancer.