Analisis profil mutasi Gen BRCA2 pada pasien kanker payudara terhadap resistansi obat kemoterapi golongan PARP Inhibitor = Analysis of BRCA2 Gene mutation profiles in breast cancer patients on resistance to PARP Inhibitor chemotherapy drugs

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Abstrak

Latar Belakang
Kanker payudara merupakan salah satu kanker paling umum pada wanita di dunia dan di Indonesia. Kanker ini dipengaruhi oleh faktor genetik dan lingkungan, dengan faktor genetiknya berupa mutasi pada gen, termasuk gen BRCA2. Kemoterapi, termasuk Poly(ADP-Ribose) Polymerase (PARP) Inhibitor, digunakan untuk mengobati kanker ini dengan cara menghambat proses perbaikan DNA yang rusak. Namun, sebagian pasien mengalami resistansi terhadap obat tersebut. Mekanisme yang mendasari proses terjadinya resistansi masih belum banyak diteliti. Penelitian deskriptif ini bertujuan untuk mengetahui profil gen BRCA2 yang bermutasi serta pengaruhnya terhadap resistansi PARP Inhibitor dengan pendekatan bioinformatika.
Metode
Penelitian dilakukan pada Januari-Oktober 2024 di Fakultas Kedokteran Universitas Indonesia. Penelitian ini menggunakan 16 sampel dari penelitian terdahulu berjudul “Raw FASTQ Data for Hotspot Regions of Cancer-Related 50 Genes Using Fresh Frozen Breast Carcinoma Tissues Obtained from IMERI-FMUI Biobank Collections” dengan accession code PRJNA820526 yang diperoleh pada 2014 hingga 2017 dan dipublikasi pada 24 Oktober 2022. Pengolahan data meliputi pengecekan kualitas data, variant calling, dan annotation gen BRCA2 serta pemodelan struktur proteinnya. Molecular docking juga dilakukan untuk melihat interaksi antara protein PARP dengan PARP Inhibitor. Hasilnya dilaporkan secara deskriptif untuk membandingkan gen normal dengan yang bermutasi. Hasil
Terdapat 0,321% varian pada sekuens dari seluruh subjek penelitian. Dua subjek (SRR18574457, SRR18574463) mempunyai mutasi BRCA2 pada daerah 3’UTR dan intron yang tidak mengubah struktur protein tersebut serta tidak mempunyai mutasi juga pada gen PARP. Tiga subjek lain (SRR18574458, SRR18574459, dan SRR18574466) mempunyai mutasi PARP4, PARP8, dan PARP9 pada daerah 3’UTR dan intron. Tidak terjadi penurunan afinitas interaksi antara protein PARP yang bermutasi dengan PARP Inhibitor.
Kesimpulan
Subjek penelitian dengan mutasi BRCA2 tidak mempunyai mutasi PARP yang menyebabkan resistansi PARP Inhibitor. Subjek penelitian dengan mutasi PARP tidak menyebabkan terjadinya penurunan afinitas interaksi dengan obat PARP Inhibitor.
.....Introduction
Breast cancer is one of the most common cancers in women in the world and in Indonesia. This cancer is caused by genetic and environmental factors, with genetic factors in the form of mutations in genes, including the BRCA2 gene. Chemotherapy, including Poly(ADP-Ribose) Polymerase (PARP) Inhibitors, is used to treat this cancer by inhibiting the process of damaged DNA reparation. However, some patients experience resistance to the drug. The mechanisms underlying the process of resistance have not yet been

widely studied. Therefore, this descriptive study aims to identify the profile of the mutated BRCA2 gene and its effect on PARP inhibitor resistance using a bioinformatics approach.
Method
The study was conducted on January-October 2024 at the Faculty of Medicine, University of Indonesia. This study used 16 samples from previous research with the title "Raw FASTQ Data for Hotspot Regions of Cancer-Related 50 Genes Using Fresh Frozen Breast Carcinoma Tissues Obtained from IMERI-FMUI Biobank Collections" with accession code PRJNA820526 which was obtained from 2014 to 2017 and published on October 24th 2022. Data processing includes checking data quality, variant calling, and annotation of the BRCA2 gene as well as modeling the protein structure. Molecular docking was also done to see the interaction between PARP protein and PARP inhibitors. The results are reported descriptively to compare normal genes with mutated ones.
Results
There was 0.321% variance in the sequences of all study subjects. Two subjects (SRR18574457, SRR18574463) had BRCA2 mutations in the 3'UTR and intron regions that did not change the structure of the protein and did not have mutations in the PARP gene either. Three other subjects (SRR18574458, SRR18574459, and SRR18574466) had PARP4, PARP8, and PARP9 mutations in the 3'UTR and intron regions. There was no decrease in the affinity of the interaction between the mutated PARP protein and the PARP inhibitor.
Conclusion
Study subjects with BRCA2 mutations did not have PARP mutations that cause PARP inhibitor resistance. Research subjects with PARP mutations did not cause a decrease in interaction affinity with PARP inhibitor drugs.