

INTISARI

HUBUNGAN PENINGKATAN KADAR INTERLEUKIN-6 SERUM POST KEMOTERAPI PERTAMA TERHADAP KEJADIAN *CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY* PADA KANKER PAYUDARA NON-METASTATIK YANG MENJALANI KEMOTERAPI BERBASIS *TAXANE*

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Latar Belakang

Chemotherapy induced peripheral neuropathy (CIPN) adalah salah satu efek samping kemoterapi. CIPN dapat menyebabkan gangguan pada fungsi sensorik, motorik dan otonom sehingga mengganggu aktivitas, menyebabkan terapi kanker tidak optimal dan mempengaruhi kualitas hidup jangka panjang pasien. Beberapa studi menunjukkan peran inflamasi pada proses kejadian CIPN. Interleukin-6 (IL-6) merupakan salah satu mediator inflamasi pada kanker payudara dan berperan pada proses kejadian CIPN. Namun hubungan sitokin tersebut terhadap kejadian CIPN post kemoterapi pertama dan kumulatif pada kanker payudara non-metastatik belum banyak dievaluasi.

Metode

Sebanyak 97 pasien yang baru terdiagnosis kanker payudara non-metastatik sejak Juli 2018 hingga Juni 2020 diikuti dalam penelitian ini. Dilakukan pengukuran kadar IL-6 serum *pre* kemoterapi dan *post* kemoterapi pertama dengan menggunakan metode ELISA. Dilakukan penilaian evaluasi CIPN di setiap siklus kemoterapi dengan skor *Common Terminology Criteria for Adverse Events* (CTCAE). Kejadian CIPN didokumentasi sebagai CIPN *post* kemoterapi pertama dan CIPN yang terjadi setiap siklus sampai kemoterapi selesai (kumulatif). Hubungan peningkatan median IL-6 *post* kemoterapi pertama terhadap kejadian CIPN *post* kemoterapi pertama dan kumulatif dianalisis dengan *wilcoxon*. IL-6 *pre* kemoterapi dikategorikan sebagai ≤ 0 pg/ml dan > 0 pg/ml. IL-6 *post* kemoterapi pertama dikategorikan sebagai $\leq 0,89$ pg/ml dan $> 0,89$ pg/ml. IL-6 *post* kemoterapi pertama, faktor demografi dan klinikopatologi yang mempengaruhi resiko kejadian CIPN *post* kemoterapi pertama dan kumulatif dianalisis univariat dengan uji *Chi-Square* atau uji *Fisher's Exact's*. Hasil analisis univariat dengan nilai $p < 0,25$ dilanjutkan dengan analisis multivariat regresi logistik.

Hasil

Terdapat peningkatan signifikan nilai median IL-6 *post* kemoterapi pertama dibandingkan *pre* kemoterapi (0,89 pg/ml vs 0 pg/ml, $p=0,000$). Kejadian CIPN *post* kemo pertama terjadi pada 18 pasien (18,6 %) sedang kejadian CIPN kumulatif terjadi pada 88 pasien (88,7%). Sebanyak 55 (51,3%) pasien mengalami onset baru CIPN dan 2 pasien mengalami progresivitas (2,3%) selama program kemoterapi. Perubahan nilai median IL-6 *post* kemoterapi pertama meningkat signifikan baik pada kelompok CIPN *post* kemoterapi pertama maupun yang tidak CIPN ($p=0,018$ dan $p=0,000$). Perubahan nilai median IL-6 *post* kemoterapi pertama meningkat signifikan pada kelompok yang mengalami CIPN kumulatif ($p=0,000$), namun meningkat tidak bermakna pada kelompok non CIPN kumulatif ($p=0,110$). Pada kelompok pasien yang mengalami CIPN *post* kemoterapi pertama terdapat 4 orang (22,2%) dengan peningkatan IL-6 *pre* kemoterapi (>0 pg/ml) dan 14 pasien (77,8%) dengan penurunan IL-6, serta terdapat 6 orang (33,3%) dengan peningkatan IL-6 *pre* kemoterapi ($>0,89$ pg/ml) dan 12 pasien (66,7%) dengan penurunan IL-6. Pada kelompok pasien yang mengalami CIPN kumulatif didapatkan 19 pasien (21,6%) dengan peningkatan IL-6 *pre* kemoterapi (>0 pg/ml) dan 69 pasien (78,4%) dengan penurunan IL-6 *pre* kemoterapi, serta terdapat 47 pasien (53,4%) dengan peningkatan IL-6 *post* kemoterapi pertama ($>0,89$ pg/ml) dan 41 pasien (46,6%) dengan penurunan IL-6 *post* kemoterapi pertama. Dalam analisis multivariat, peningkatan IL-6 *post* kemoterapi pertama tidak berhubungan terhadap kejadian CIPN baik *post* kemoterapi pertama maupun CIPN kumulatif (*odds ratio* (OR) OR 0,449; 95% IK 0,150-1,343; $p = 0,152$ dan OR 4,695, 95% . IK 0,797-27,668; $p = 0,087$)

Simpulan

Terdapat peningkatan signifikan median IL-6 *post* kemoterapi pertama dibandingkan *pre* kemoterapi. Proporsi perubahan nilai median ini secara signifikan terjadi baik pada pasien yang menderita CIPN *post* kemoterapi pertama, pasien non CIPN *post* kemoterapi pertama, serta pasien CIPN kumulatif. Namun demikian, dalam analisis multivariat, peningkatan kadar IL-6 *post* kemoterapi pertama tidak menunjukkan hubungan signifikan terhadap kejadian CIPN pada subjek penelitian ini, baik CIPN *post* kemoterapi pertama maupun CIPN kumulatif.

Kata kunci: kanker payudara, IL-6, inflamasi, CIPN

ABSTRACT

ASSOCIATION OF POST-FIRST-CYCLE CHEMOTHERAPY SERUM INTERLEUKIN -6 INCREASE WITH CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN NON-METASTATIC BREAST CANCER PATIENTS RECEIVING TAXANE-BASED CHEMOTHERAPY

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Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy. CIPN can cause impairments in sensory, motor, and autonomic functions, leading to disruptions in daily activities, suboptimal cancer treatment, and long-term reductions in patients' quality of life. Several studies have suggested that inflammation plays a role in the pathogenesis of CIPN. Interleukin-6 (IL-6) is an inflammatory mediator involved in breast cancer and is implicated in the development of CIPN. However, the relationship between this cytokine and the occurrence of early and cumulative CIPN in non-metastatic breast cancer patients has not been extensively evaluated

Methods

This study included 97 newly diagnosed non-metastatic breast cancer patients between July 2018 and June 2020. Serum IL-6 levels were measured pre-chemotherapy and after the first chemotherapy cycle using the ELISA method. CIPN was evaluated at each chemotherapy cycle using the Common Terminology Criteria for Adverse Events (CTCAE) scoring system. CIPN incidence was recorded as early CIPN (post-first chemotherapy) and cumulative CIPN (occurring at any cycle until chemotherapy completion). The association between median IL-6 changes before and after the first chemotherapy cycle with early and cumulative CIPN incidence was analyzed using the Wilcoxon test. C Pre-chemotherapy IL-6 levels were categorized as ≤ 0 pg/mL and > 0 pg/mL. Post-first-cycle chemotherapy IL-6 levels were categorized as ≤ 0.89 pg/mL and > 0.89 pg/mL. Post-first-cycle IL-6 levels, along with demographic and clinicopathological factors associated with the risk of chemotherapy-induced peripheral neuropathy (CIPN) after the first cycle and cumulatively, were analyzed using univariate analysis via the Chi-Square test

or Fisher's Exact test. Variables with a p-value < 0.25 in univariate analysis were subsequently included in a multivariate logistic regression analysis

Results

There was a significant increase in median serum IL-6 levels after the first chemotherapy cycle compared to pre-chemotherapy levels (0.89 pg/mL vs. 0 pg/mL, $p = 0.000$). Early CIPN occurred in 18 patients (18.6%), while cumulative CIPN was observed in 88 patients (88.7%). Fifty-five patients (51.3%) experienced new-onset CIPN, and 2 patients (2.3%) showed progression of neuropathy during chemotherapy program. The increase in median IL-6 levels after the first chemotherapy cycle was significant in both the early CIPN group and the non-CIPN group ($p = 0.018$ and $p = 0.000$, respectively). Median IL-6 levels also increased significantly in the cumulative CIPN group ($p = 0.000$), but the increase was not statistically significant in the non-cumulative CIPN group ($p = 0.110$). In the group of patients who developed CIPN after the first cycle of chemotherapy, 4 patients (22.2%) had elevated pre-chemotherapy IL-6 levels (>0 pg/mL), while 14 patients (77.8%) had decreased IL-6 levels. Additionally, 6 patients (33.3%) had elevated post-chemotherapy IL-6 levels (>0.89 pg/mL), and 12 patients (66.7%) had decreased IL-6 levels. Among patients who experienced cumulative CIPN, 19 patients (21.6%) had elevated pre-chemotherapy IL-6 levels (>0 pg/mL), while 69 patients (78.4%) had decreased levels. Furthermore, 47 patients (53.4%) exhibited elevated post-first-cycle IL-6 levels (>0.89 pg/mL), whereas 41 patients (46.6%) showed decreased levels. In multivariate analysis, increased IL-6 levels after the first chemotherapy cycle were not significantly associated with the occurrence of either post-first-cycle CIPN or cumulative CIPN (odds ratio [OR] 0.449; 95% confidence interval [CI]: 0.150–1.343; $p = 0.152$, and OR 4.695; 95% CI: 0.797–27.668; $p = 0.087$, respectively).

Conclusion:

This study demonstrated a significant increase in median IL-6 levels following the first cycle of chemotherapy compared to pre-chemotherapy levels. The proportion of this change in median values was statistically significant across all patient subgroups, including those who developed chemotherapy-induced peripheral neuropathy (CIPN) after the first cycle, those who did not develop CIPN, and those with cumulative CIPN. However, in the multivariate analysis, elevated IL-6 levels after the first chemotherapy cycle were not significantly associated with the occurrence of CIPN in this study population, either after the first chemotherapy cycle or cumulatively.

Keyword: breast cancer, IL-6, inflammation, CIPN