HUBUNGAN ANTARA EKSPRESI PROTEIN CASPASE 3 DENGAN OPERABILITAS KANKER SERVIKS STADIUM IIA2 DAN IIB
POST KEMOTERAPI NEOADJUVAN DI RSUP DR SARDJITO YOGYAKARTA
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ABSTRAK

LATAR BELAKANG: Kanker serviks merupakan salah satu kanker pada perempuan yang memiliki angka kejadian dan kematian yang tinggi di Indonesia. Pada kanker serviks stadium IIA2 dan IIB dikenal modalitas kemoterapi neoadjuvan sebelum operasi radikal yang bertujuan untuk mengurangi massa tumor sehingga memudahkan pembedahan dan menghambat mikrometastasis. Infeksi Human Papilloma Virus (HPV) merupakan faktor penting penyebab kanker serviks. Protein *caspase 3* yang berperan dalam proses apoptosis berkaitan dengan patogenesis kanker serviks. Sampai saat ini, belum ada prediktor yang dapat digunakan untuk memprediksi tingkat operabilitas kanker serviks stadium IIA2 dan IIB setelah pemberian kemoterapi neoadjuvan.

TUJUAN: Mengetahui hubungan antara ekspresi *caspase 3* dengan operabilitas kanker serviks stadium IIA2 dan IIB post kemoterapi neoadjuvan di RSUP Dr. Sardjito Yogyakarta.

MATERIAL DAN METODE: Penelitian ini menggunakan metode kohort retrospektif melibatkan 32 pasien yang memenuhi kriteria inklusi. Blok parafin jaringan serviks dilakukan pengecatan imunohistokimia dengan menggunakan antibodi *caspase 3*. Kelompok penelitian terdiri dari ekspresi *caspase 3* positif dan negatif. Setelah dilakukan kemoterapi neoadjuvan dilakukan pemeriksaan secara klinis untuk menentukan operabilitas. Variabel luar yang dievaluasi adalah stadium kanker, jenis histopatologi, derajat diferensiasi dan regimen kemoterapi. Analisis data menggunakan uji Chi square dan uji regresi logistik.

HASIL: Dari 32 subyek penelitian didapatkan rerata usia pasien 53,06 tahun, seluruh subyek memiliki paritas ≥1 anak. Berdasarkan operabilitas terdapat 9 pasien (28,13%) operabel dan 23 pasien (71,88%) inoperabel, dimana 19 pasien (59,38%) menunjukkan ekspresi *caspase 3* positif dan 13 pasien (40,3%) menunjukkan ekspresi *caspase 3* negatif. Dari hasil analisis bivariat didapatkan ekspresi *caspase 3* positif bermakna secara statistika dalam operabilitas kanker serviks post kemoterapi neoadjuvan. Ekspresi *caspase 3* positif 5,47 kali lebih operabel dibandingkan dengan ekspresi *caspase 3* negatif (p=0,050; RR 5,474; CI 95% 0,774-38,685). Berdasarkan hasil analisis multivariat ekspresi *caspase 3* tidak berbeda bermakna secara statistika dalam mempengaruhi operabilitas kanker serviks stadium IIA2 dan IIB terhadap kemoterapi neoadjuvan (p=0,268; RR 4,071; CI 95% 0,919-16,740), namun secara klinis ekspresi *caspase 3* positif lebih operabe empat kali dibandingkan *caspase 3* negatif.

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KESIMPULAN: Ekspresi *caspase 3* positif empat kali lebih operabel dibandingkan dengan ekspresi *caspase 3* negatif pada kanker serviks stadium IIA2 dan IIB post kemoterapi neoadjuvan.

KATA KUNCI: ekspresi *caspase 3*, kanker serviks stadium IIA2 dan IIB, kemoterapi neoadjuvan, operabilitas.

ABSTRACT

BACKGROUND: Cervical cancer is a cancer in women that has a high incidence and mortality in Indonesia. In stage IIA and IIB cervical cancer, neoadjuvant chemotherapy modality is known before radical surgery which aims to reduce tumor mass to facilitate surgery and inhibit micrometastatic. Human Papilloma Virus (HPV) infection is an important factor in causing cervical cancer. Caspase 3 protein which plays a role in the apoptosis process related to the pathogenesis of cervical cancer. Nowadays, there are no predictors that can be used to predict the operability rate of stage IIA2 and IIB cervical cancer after presenting neoadjuvant chemotherapy.

PURPOSE: To determine the relationship between caspase 3 expression and the operability of stage IIA2 and IIB cervical cancer after neoadjuvant chemotherapy at Dr. Sardjito Hospital Yogyakarta.

MATERIAL AND METHOD: This study used a retrospective cohort method involving 32 patients who met the inclusion criteria. The tissue paraffin block was stained immunohistochemistry using caspase 3 antibody. The research group consisted of positive and negative caspase 3 expressions. After chemotherapy, neoadjuvant is performed clinically to determine operability. The external variables that were evaluated were cancer stage, histopathology type, grade of differentiation and chemotherapy regimen. Data analysis used Chi square test and logistic regression test.

RESULTS: Of the 32 study subjects, the mean age of the patients was 53.06 years, all subjects had parity ≥1 child. Based on operability, there were 9 patients (28.13%) operable and 23 patients (71.88%) inoperable, where 19 patients (59.38%) showed positive caspase 3 expression and 13 patients (40.3%) showed negative caspase 3 expression. From the bivariate analysis, it

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was found that caspase 3 expression was statistically positive in cervical cancer operability after neoadjuvant chemotherapy. Positive caspase 3 expression was 5.47 times more operable than negative caspase 3 expression (p = 0.050; RR 5.474; 95% CI 0.774-38.685). Based on the results of multivariate analysis, caspase 3 expression did not differ statistically in affecting the operability of stage IIA2 and IIB cervical cancer against neoadjuvant chemotherapy (p=0,268; RR 4,071; CI 95% 0,919-16,740), but clinically, caspase 3 was positive more operable four times than caspase 3 negative.

CONCLUSION: Positive caspase 3 expression is four times more operable than negative caspase 3 expression in stage IIA2 and IIB cervical cancer after neoadjuvant chemotherapy.

KEYWORDS: caspase 3 expression, stage IIA2 and IIB cervical cancer, neoadjuvant chemotherapy, operability.

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DAFTAR SINGKATAN

AIF	Apoptosis inducing factor
APAF 1	Apoptotic Protease Activating Factor-1
ATM-ATR	Ataxia-telangiectasia mutated, ATM and Rad3-related
BAD	Bcl-2 Antagonist of Cell Death
Bak	Bcl-2 antagonist/ killer
Bax	Bcl-2 Associated X-protein
Bcl-B	Bcl-2 like protein 10
Bcl-2	B-Cell Lymphoma 2
Bcl-2 L1	Bcl-2 like protein 1
Bcl-xL	B-Cell Lymphoma-extra Large
Bcl-W	Bcl-2 like protein 2
BCL2L2	Bcl-2 like protein 2
BFL-1	Bcl-2 related protein A1
BH Domain	Bcl-2 homology domain
BID	BH3-interacting domain death agonist
BIK	Bcl-2 interacting killer
BIM	Bcl-2 interacting mediator of cell death
Caspase	Cysteine dependent aspartate directed proteases
CCRT	Concurrent platinum based chemoradiation
CDC	Centers for Disease Control
CDH1	Cadherin1
CDH2	Cadherin2
CDKN2A	Cyclin dependent kinase inhibitor 2A
CD95	Cluster of differentiation 95
CHK2	Checkpoint kinase 2
CI	Confident Interval
C-IAP2	Cellular inhibitor of apoptosis 2
CIN	Cervical intraepithelial neoplasma
CT	Computed tomography
CYFRA 21-1	Cytokeratin-19 fragment
DAB	Diamino Benzidine
DATP	Deoxyadenosine triphosphate
DI	Daerah Istimewa
DIC	Disseminated intravascular coagulation
DISC	Death inducing signaling complex
DNA	Deoxyribonucleic acid
E-cadherin	Epithelial-cadherin
ERK1	Extracellular signal regulated kinases 1
ESMO	European Society for Medical Oncology
FADD	Fas Associated protein with Death Domain
FasL	Fas Ligand
FIGO	The International Federation of Gynecology and Obstetrics
HPV	Human Papiloma Virus

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HTR2	Human serotonin receptor
HSCORE	Histological Score
ICU	Intensive Care Unit
IGF2	Insulin like growth factor 2
IHC	Immunohistochemistry
IL	Interleukin
IVP	Intravenous pyelogram
Litbangkes	Badan Penelitian dan Pengembangan Kesehatan
MDM2	Mouse double minute 2
MMP2	Metaloproteinase matriks 2
MOM	Mitochondrial outer membrane
MOMP	Mitochondrial outer membrane permeabilization
MRI	Magnetic Resonance Imaging
MYC	Myelocytomatosis
NACT	Neoadjuvant Chemotherapy
NF-kappa-B	Nuclear factor kappa B
NK cell	Natural Killer cell
Nm23-h1	Nucleoside diphosphate Kinase 1
OS	Overall survival
PA	Patologi anatomi
PAK-2	p21-activated kinase 2
PARP	Poly ADP ribose polymerase
PBS	Phosphate buffered saline
PET	Positron Emission Tomography
PFS	Progression free survival
PKC	Protein kinase C
PRb	Protein Rb
PUMA	p53 upregulated modulator of apoptosis
P53	Tumor protein P53
P65	Tumor protein P65
RADD	Receptor Associated Death Domain
RI	Republik Indonesia
RSUP	Rumah Sakit Umum Pusat
SAMC	S-adenosylmethionine carrier
SCC	Squamous cell carcinoma
USG	Ultrasonografi
TIMP2	Tissue inhibitor of metalloproteinase 2
TRAIL	TNF related apoptosis inducing ligand
TRADD	TNF receptor 1 associated death domain protein
VEGF-C	Vascular endhotelial growth factor
WHO	World Health Organization
XIAP	X-linked inhibitor of apoptosis protein