Peran Simvastatin dalam Menghambat Migrasi dan Proliferasi Sel Kanker Payudara untuk Mencegah Metastasis Melalui Sinyal Rho/Rho-Associated Coiled-Coil Containing Protein Kinase = The Role of Simvastatin in Inhibiting Migration and Proliferation of Breast Cancer Cells through Rho/Rho-Associated Coiled-Coil- Containing Protein Kinase Signal

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Abstrak

Karsinoma payudara (KPD) merupakan kanker terbanyak pada perempuan dan lebih dari 90%
kematian akibat kanker diebabkan oleh adanya metastasis. Diperlukan terapi yang tidak hanya
fokus pada proliferasi, tetapi juga fokus pada proses metastasis. Jalur Rho/ROCK diketahui
memengaruhi invasi dan metastasis. Studi terbaru menunjukkan bahwa jalur Rho/ROCK
berperan penting pada regulasi migrasi dan proliferasi sel, sehingga dapat dijadikan target
terapi. Selain mereduksi biosintesis kolesterol melalui inhibisi 3-hydroxy-3-methylglutaryl
coenzyme A reductase, statin juga mengurangi formasi isoprenoid intermediates yang
diperlukan untuk mediasi pensinyalan melalui jalur Rho/ROCK. Statin diduga dapat
menghambat jalur Rho/ROCK dan aman digunakan dalam jangka panjang. Penelitian ini
bertujuan untuk mengetahui efek antimetastasis (migrasi dan proliferasi) simvastatin terhadap
KPD melalui jalur Rho/ROCK.
Penelitian ini merupakan uji intervensi perioperative “window”, parallel unmatching,
randomized, double-blinded, dan placebo-controlled yang berlangsung sejak November 2014
hingga Juli 2015. Sebanyak 30 pasien KPD diberikan terapi simvastatin 40 mg/hari dan plasebo
selama 4-6 minggu lalu dilakukan mastektomi di RSCM, RSPAD Gatot Subroto, RS
Persahabatan, dan RSUD Koja. Perubahan migrasi (indeks migrasi, aktivitas ROCK dan kadar
mRNA RhoC, CXCR4, dan CD44) dan reduksi proliferasi (ekspresi Ki67) yang didapat dari
jaringan biopsi dan mastektomi dievaluasi sebelum dan sesudah terapi. Kemudian karakteristik
yang berbeda bermakna dianalisis juga hubungannya dengan kadar kolesterol darah, grade,
status ER/PR, dan status HER-2.
Simvastatin 40 mg/harimenurunkan indeks migrasi (p=0,006), aktivitas ROCK (p=0,002), kadar
mRNA CXCR4 (p=0,045) dan ekspresi Ki67 (p<0,001) secara bermakna. Terdapat tren
penurunan kadar mRNA RhoC (p=0,163) dan CD44 (p=0,094). Penurunan aktivitas ROCK
berhubungan dengan kolesterol tinggi (p=0,008), grade rendah (p=0,019) dan amplifikasi HER-
2 (p=0,009). Penurunan kadar mRNA CXCR4 berhubungan dengan kolesterol tinggi (p=0,024),
ER/PR positif (p=0,013), dan amplifikasi HER-2 (p=0,018). Penurunan ekspresi Ki67
berhubungan dengan kolesterol tinggi (p=0,001), grade rendah (p=0,017) dan tinggi (p=0,018),
HER-2 (p=0,002) dan negatif (p=0,034), serta ER/PR positif (p=0,007) dan negatif (p=0,042).
Simvastatin dapat menginhibisi migrasi dan menyupresi proliferasi pada KPD melalui jalur
Rho/ROCK, sehingga dapat digunakan sebagai terapi pencegahan metastasis kanker payudara. <hr /> Breast cancer is the most common cancer among women and more than 90% of cancer
deaths are caused by metastasis. There is an urgent need for the development of therapeutic
intervention specifically targeted to the metastatic process. The Rho/ROCK pathway is
found to be involved in invasion and metastasis. Recent studies have revealed that the
Rho/ROCK pathway plays a

critical role in regulation of cancer cell migration and
proliferation, making it a potential therapy target. Besides reducing cholesterol biosynthesis
by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, statins also decrease the
formation of isoprenoids intermediates essential for mediating the Rho/ROCK signalling.
Statin is thought to inhibit the Rho/ROCK pathway and is safe for long-term use. This study
aimed to determine the antimetastasis (migration and proliferation) effect of simvastatin on
breast cancer through the Rho/ROCK pathway.
In a parallel unmatching, randomized, double-blinded, placebo-controlled, perioperative
“window” interventional trial conducted from November 2014 until July 2015, 30 breast
cancer subjects were treated with simvastatin 40 mg/day or placebo for 4–6 weeks
followed by mastectomy (n=15 in each arm) at Cipto Mangunkusumo Hospital, Gatot
Subroto Army Hospital, Persahabatan Hospital and Koja Hospital. Changes in
migration (migration index, ROCK activity, mRNA RhoC, CXCR4 and CD44 level)
and proliferation (Ki67 expression) from biopsy and final surgical specimen were
obtained before and after intervention. The relationships of significant factors with
blood cholesterol level, grade, ER/PR and HER-2 status were analyzed.
Simvastatin 40 mg/d significantly reduced migration index (p = 0.006), ROCK activity
(p = 0.002), mRNA CXCR4 level (p = 0.045) and reduced Ki67 expression (p < 0.001).
Decreased was also observed for mRNA RhoC (p = 0.163) and CD44 level (p = 0.094).
Reduced ROCK activity was related to high cholesterol level (p = 0.008), low grade (p
= 0.019) and HER-2 amplification (p = 0.009). Reduced CXCR4 transcription was
related to high cholesterol level (p = 0.024), positive ER/PR (p = 0.013) and HER-2
amplification (p = 0.018). Ki67 expression was related to high cholesterol level (p =
0.001), low (p = 0.017) and high grade (p= 0.018), with (p = 0.002) and without HER-2
amplification (p = 0.034), and positive (p = 0.007) and negative (p = 0.042) ER/PR
status.
Simvastatin inhibits the migration and proliferation in breast cancer through Rho/ROCK
pathway, hence holds a promising potential as prophylaxis for breast cancer metastasis</p>