MANFAAT MODEL PROGNOSIS METASTASIS KE OTAK PADA WANITA PENDERITA KANKER PAYUDARA UNTUK PENGELOLAAN KLINIS

DISERTASI

Untuk Memenuhi Sebagian Persyaratan
Mencapai Derajat Doktor S-3

Minat Bidang Kedokteran Klinik
Fakultas Kedokteran Program Doktor

Diajukan oleh

Rini Andriani
09/295443/SKU/00319

Kepada

PROGRAM DOKTOR
FAKULTAS KEDOKTERAN
UNIVERSITAS GADJAH MADA
YOGYAKARTA
2016

LEMBAR PERSETUJUAN

MANFAAT MODEL PROGNOSIS METASTASIS KE OTAK PADA WANITA DENGAN KANKER PAYUDARA UNTUK PENGELOLAAN KLINIS

Diajukan Oleh:

Rini Andriani
09/295443/SKU/00319

Telah Disetujui Oleh:

Pembimbing I

Prof. Dr. dr. Samekto Wibowo, P.Far.K, Sp.FK (K), SpS (K) Tanggal.....

Pembimbing II

Prof. Dr. dr. Teguh Aryandono, Sp.B (K) Onk Tanggal.....

Pembimbing III

Prof. dr. Siswanto Agus Wilopo, SU., M.Sc., Sc.D. Tanggal.....

ABSTRACT

Background: Brain metastasis from the breast cancer (BMBC) is the biggest challenge for neuro-oncologist since limited of availabilities on management and treatment for breast cancer (BC) patients. The problem is whether the identification of prognostic factors and the construction of prognostic model can help to screen and clinical management for BMBC patient?

Goal and Objectives: The goal of this research to improve survival of BC patient by identifying prognostic factors for time of development of BMBC in Indonesian women. The objectives of this study: a) to describe epidemiology, management and prognostic factors of BMBC; b) identification main prognostic for BMBC and construct prognostic models for improving effectiveness and efficiencies of clinical management; c) evaluate sensitivity and specificity of α β crystallin as biomarkers for predicting time for the development of BMBC.

Study Design: Phase one of this study is a cohort retrospective design to identify factors which are available and can be collected for prognostic model construction. Second phase is assessing prognostic factors and modelling using prospective cohort study. The third phase is a cross-sectional design by selecting case and control for testing the use of biomarker α β crystallin.

Settings: All phases of this study were conducted on BC patients admitted at Dharmais National Cancer Hospital, Jakarta.

Samples: First phase of the study is a followed-up retrospectively on 215 BC without BMBC ages 25-75 who were attending hospital from January 1, 2010 to August 31, 2010. Second phase of study followed-up prospectively for 516 BC without BMBC ages 25-75 who were attending hospital from January 1, 2013 to December 31, 2013. For the end of follow-up for the first phase was August 31, 2012 and the second phase was July 31, 2015 so that we recorded event of BMBC, death, or lost to follow-up. On the third phase, 62 sub-samples were examined of the biomarker α β crystallin status among with and without BMBC.

Prognostic Factors: In addition to tumor subtype, the study collected data on surgery, chemotherapy, hormonal therapy and radiation to primary tumor and other risk factors, such as tumor subtype, expression of α β crystallin, metastases to extra cranial, age, stadium and tumor grade.

Study Outcomes: The dependent variable of this study is the time since diagnosed BC until BMBC event. Risk factors identification used Cox's regression to obtain relative risk (RR) estimates and biomarkers tested using values of sensitivity and specificity for BMBC diagnosis.

Results: This is a first report on cumulative incidence of BMBC among BC patients using prospective design in Indonesia where the incidence of BMBC is reported as 15-20%. According to epidemiological profiles, BMBC are commonly found among younger women (age below 40 years), high school graduate or higher, and the hospital payment using insurance. A tumor subtype of Luminal A

has higher percentage (48%) where HER2 subtype is lowest (11.7%) in Indonesia. This study found risks of having BMBC as follows: age at the time of BC diagnosed, tumor subtype (tests ER, PR and HER2 receptor), grade, stadium and metastases extracranial (lung, liver, bone). The best prognostic model (R^2 >15%) for the time to the development of BMBC using those factors has RR 2.6 to 8.8 which are statistically significant. Our first test of α β crystallin using method 1 can be performed with reliable result. Degree of agreement on the biomarkers examination among two pathologists was considered fair which resulted Kappa (95% confidence intervals) is 0.645 (0.463-0.827). Result of the α β crystallin examination using method 1 has high sensitivity and specificity, which are 77 and 65 percent respectively. Using method 2 (H-score), resulted high sensitivity and specificity but depend on the cut of point normality. For that reason, selection of cut-point on normality should be decided according to goal or screening or diagnosis, whether to reduce false positive or false negative result.

Conclusion and Recommendation: Breast cancer patient can be screened using prognostic model at the earlier stage of care. A high risk of patient found should be followed by testing of α β crystallin. Patients with high risk according to prognostic model but negative on α β crystallin test can be considered as low risks for BMBC. It is recommended that patients with high risk according to prognostic model and positive on α β crystallin test has to go for MRI or CT scan examination for further assessment of BMBC. Need further study on the use of α β crystallin test for routine screening BMBC on BC patients so that the clinical management can be performed earlier.

Key Words: Survival time - Breast Cancer - Brain Metastases - Women - Prognostic Model-Clinical Pathways