Studi pengaruh computational settings terhadap tingkat akurasi single timepoint dosimetry pada kasus late timepoint menggunakan metode NLME dan model PBPK = Study of the effect of computational settings on the accuracy level of single timepoint dosimetry in case of late timepoint using NLME method and PBPK model

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Abstrak

Neuroendocrine tumors (NETs) merupakan tumor yang berasal dari sel-sel neuroendokrin dan dapat diobati menggunakan Peptide-Receptor Radionuclide Therapy (PRRT). PRRT memiliki tujuan untuk memastikan aktivitas radiofarmaka yang tinggi pada sel tumor dan rendah pada organ at risk. Model Physiologically Based Pharmacokinetics (PBPK) sangat baik untuk analisis, simulasi, dan prediksi biodistribusi dari radiofarmaka yang diberikan. Penelitian ini menggunakan metode fitting Nonlinear Mixed Effect (NLME) pada parameter PBPK dari pasien PRRT. Pilihan starting value yang tepat membantu mengurangi risiko menemukan local minimum berdasarkan estimasi Objective Function (OF) sehingga diperoleh fitting yang baik. Penelitian ini bertujuan menganalisis pengaruh starting value terhadap tingkat akurasi Single Timepoint Dosimetry pada late timepoint menggunakan model PBPK dan metode NLME. Penelitian ini terbatas pada pasien terdiagnosis NETs dan meningioma menggunakan pengobatan PRRT. Proses pengukuran pre-terapi pada 8 pasien menggunakan radiofarmaka 111In- DOTATATE untuk mengetahui biokinetik pasien dengan aktivitas sekitar 140 ± 14 MBq (jumlah total peptida 75 ± 10 nmol) yang diinjeksi secara intravena. Parameter yang diestimasi terdiri dari densitas reseptor organ (Ri), release rate normal tissue (NT,release), perfusi tumor (fTU), dan linear binding rate dari protein serum (KonAlb). Dua teknik dilakukan dalam penelitian ini yaitu, Full Timepoint Dosimetry (FTD) dan Single Timepoint Dosimetry (STD). FTD dilakukan menggunakan 5 timepoint yang berbeda, sedangkan untuk STD dilakukan pada 2 timepoint terakhir yaitu, timepoint 4 (T4) dan timepoint 5 (T5). Perubahan starting value hanya diberikan untuk parameter reseptor densitas ginjal (RK) dan perfusi tumor (ftu) pada STD yang divariasikan (STD(V,T)). Variasi starting value yang diberikan adalah 100 (V1), 10 (V2), 5 (V3), 2 (V4), 1/2 (V5), 1/5 (V6), 1/10 (V7), dan 1/100 (V8) kali dari nilai awal. Total fitting dilakukan sebanyak 145 kali dengan FTD berjumlah 1 kali, STD awal 16 kali. Time-Integrated Activity Coefficients (TIACs) yang diperoleh dari hasil simulasi FTD dan STD(0,T) akan ditinjau dengan Relative Deviation (RD). RD juga dilakukan untuk simulasi STD(V,T) terhadap STD(0,T). RD dikatakan baik apabila hasil yang diperoleh <10%. Rata-rata RD STD(0,T4) terhadap FTD memiliki nilai untuk organ ginjal (5±7)%, organ limfa (7±9)%, organ hati (-4±6)%, tumor (8±8)%, dan seluruh tubuh (11±13)%. Rata-rata RD STD(0,T5) terhadap FTD memiliki nilai untuk organ ginjal (-2±7)%, organ limfa (6±11)%, organ hati (-9±8)%, tumor (7±22)%, dan seluruh tubuh (3±8)%. Variasi V2, V3, V4, V5, dan V6 pada STD untuk T4 dan T5 memiliki RD <10%. Rentang variasi starting value untuk parameter densitas reseptor ginjal (RK) 5.57 x 105 nmol.L-1 - 2.79 x 107 nmol.L-1 dan untuk paramter perfusi tumor (ftu) adalah 8.67 x 10-3 mL.min-1.g-1 - 4.53 x 10-1 mL.min-1.g-1. Hasil dari penelitian ini menunjukkan bahwa STD yang divariasikan memiliki threshold 10 sd. 1/5 kali nilai awal.

.....Neuroendocrine tumors (NETs) are tumors derived from neuroendocrine cells and can be treated using Peptide-Receptor Radionuclide Therapy (PRRT). PRRT aims to ensure high radiopharmaceutical activity in

tumor cells and low in organ at risk. The Physiologically Based Pharmacokinetics (PBPK) model is excellent for analysis, simulation, and prediction of the biodistribution of a given radiopharmaceutical. This study uses the Nonlinear Mixed Effect (NLME) fitting method on the PBPK parameters of the patient's PRRT. Choosing the right starting value helps reduce the risk of finding the minimum locale based on the estimated Objective Function (OF) so that a good fit is obtained. This study aims to analyze the effect of starting values on the accuracy of Single Timepoint Dosimetry at late time points using the PBPK model and the NLME method. This study was limited to patients diagnosed with NETs and meningiomas using PRRT treatment. The process of pre-therapy measurement in 8 patients using radiopharmaceutical 111In-DOTATATE to determine the biokinetics of patients with an activity of about 140 ± 14 MBq (total amount of peptide 75 ± 10 nmol) which was injected intravenously. The estimated parameters consisted of organ receptor density (Ri), normal tissue release rate (NT,release), tumor perfusion (ftu), and linear binding rate of serum protein (KonAlb). Two techniques were used in this study, namely, Full Timepoint Dosimetry (FTD) and Single Timepoint Dosimetry (STD). FTD is performed using 5 different timepoints, while for STD it is carried out at the last 2 timepoints, namely, timepoint 4 (T4) and timepoint 5 (T5). Changes in the starting values were only given for the parameters of kidney density receptor (RK) and tumor perfusion (ftu) in the STD varied (STD(V,T)). The initial value variations given are 100 (V1), 10 (V2), 5 (V3), 2 (V4), 1/2 (V5), 1/5 (V6), 1/10 (V7), and 1/ 100 (V8) times the starting value. A total of 145 fittings were performed with FTD opened once, initial STD 16 times (STD(0,T)), and STD varied (STD(V,T)) 128 times. Time-Integrated Activity Coefficients (TIACs) obtained from FTD and STD(0,T) simulation results will be reviewed with Relative Deviation (RD). RD was also performed to simulate STD(V,T) against STD(0,T). RD is said to be good if the results obtained are <10%. The mean RD STD(0,T4) against FTD had values for kidney (5±7)%, lymph (7±9)%, liver (-4±6)%, tumor (8±8)% , and whole body (11±13)%. The mean RD STD(0,T5) against FTD had values for kidney (-2±7)%, lymph (6±11)%, liver (-9±8)%, tumors (7±22) %, and whole body (3±8)%. Variations V2, V3, V4, V5, and V6 on STD for T4 and T5 had RD <10%. The range of variation of the starting value for the kidney receptor density (RK) parameter is 5.57 x 105 nmol.L-1 - 2.79 x 107 nmol.L-1 and for the tumor perfusion parameter (ftu) is 8.67 x 10-3 mL.min-1. g-1 - 4.53 x 10-1 mL.min-1.g-1. The results of this study indicate that the STD which is varied has a threshold of 10 sd. 1/5 times the initial value.