Everolimus exposure and early metabolic response as predictors of treatment outcomes in breast cancer patients treated with everolimus and exemestane

Annelieke E.C.A.B. Willemsen[1], Lioe-Fee de Geus-Oei[2,3], Maaike de Boer[4], Jolien Tol[5], Yvonne Kamm[6], Paul C. de Jong[7], Marianne A. Jonker[8], Allert H. Vos[9], Willem Grootjans[2], Johannes W.B. de Groot[10], Sasja F. Mulder[1], Erik H.J.G. Aarntzen[11], Winald R. Gerritsen[1], Carla M.L. van Herpen[1], Nielka P. van Erp[12]*

[1]Department of Medical Oncology, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands

[2]Department of Radiology, Leiden University Medical Center (LUMC), Leiden, the Netherlands

[3]Biomedical Photonic Imaging Group, MIRA Institute, University of Twente, Enschede, the Netherlands

[4]Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands

[5]Department of Medical Oncology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands

[6]Department of Medical Oncology, Maasziekenhuis Pantein, Boxmeer, the Netherlands

[7]Department of Medical Oncology, St. Antonius Ziekenhuis, the Netherlands

[8]Department for Health Evidence, Radboud university medical center, Nijmegen, the Netherlands

[9]Department of Medical Oncology, Bernhoven Ziekenhuis, Uden, the Netherlands

[10]Isala Oncology Center, Zwolle, the Netherlands

[11]Department of Radiology and Nuclear Medicine, Radboud university medical center, Nijmegen, the Netherlands

[12]Department of Pharmacy, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands

*Corresponding author:
Nielka P. van Erp, PharmD, PhD.
Department of Pharmacy, Radboud Institute for Health Sciences, Radboud university medical center
P.O. Box 9101, 6500 HB Nijmegen, the Netherlands
Nielka.vanerp@radboudumc.nl
Telephone: 0031-243617744.

Running heading: Everolimus exposure and FDG-PET to predict everolimus outcomes

Everolimus exposure and early metabolic response as predictors of treatment outcomes in breast cancer patients treated with everolimus and exemestane

Annelieke E.C.A.B. Willemsen[1], Lioe-Fee de Geus-Oei[2,3], Maaike de Boer[4], Jolien Tol[5], Yvonne Kamm[6], Paul C. de Jong[7], Marianne A. Jonker[8], Allert H. Vos[9], Willem Grootjans[2], Johannes W.B. de Groot[10], Sasja F. Mulder[1], Erik H.J.G. Aarntzen[11], Winald R. Gerritsen[1], Carla M.L. van Herpen[1], Nielka P. van Erp[12]*

[1]Department of Medical Oncology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands.
[2]Department of Radiology, Leiden University Medical Center (LUMC), Leiden, the Netherlands.
[3]Biomedical Photonic Imaging Group, MIRA Institute, University of Twente, Enschede, the Netherlands.
[4]Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands.
[5]Department of Medical Oncology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands.
[6]Department of Medical Oncology, Maasziekenhuis Pantein, Boxmeer, the Netherlands.
[7]Department of Medical Oncology, St. Antonius Ziekenhuis, the Netherlands.
[8]Department for Health Evidence, Radboud University Medical Center, Nijmegen, the Netherlands.
[9]Department of Medical Oncology, Bernhoven Ziekenhuis, Uden, the Netherlands.
[10]Isala Oncology Center, Zwolle, the Netherlands.
[11]Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.
[12]Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands.

*Corresponding author:
Nielka P. van Erp, PharmD, PhD.
Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center
P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.
Nielka.vanerp@radboudumc.nl
Telephone: 0031-243617744.

Running heading: Everolimus exposure and FDG-PET to predict everolimus outcomes

Materials and methods

FDG-PET aquisition and analysis

FDG-PET images were acquired using dedicated PET/CT scanners. We used the same scanner for each patient for the baseline scan and the follow-up scans. Serum glucose was measured before start of the scan. FDG (1.6 MBq/kg) was administered intravenously, and image acquisition was started 50-70 minutes post-injection. An emission scan was performed from the skull to the proximal thigh, in combination with a low dose CT scan for anatomical correlation and attenuation correction.

Using Inveon Research Workplace 4.1 Software (Preclinical Solutions, Siemens Medical Solutions USA, Knoxville Tennessee, USA) software, loosely fitting regions of interest covering the whole tumor were semi-automatically drawn over visually discernible hypermetabolic lesions by one dedicated physician. We measured the activity in Bq/ml and converted this to standardized uptake values normalized by lean body weight (SUL), using the formula of Janmahasatian (1). The SUL_{peak} was calculated using a customized Matlab script (Matlab 2014b, Natick, Massachusetts, USA), that searched automatically for the metabolically most active part of a lesion using a three-dimensional spherical volume of interest (VOI) of 1 cm^3. A maximum of five lesions with the highest SUL_{peak} were chosen as target lesions, with a maximum of two lesions per organ. In the follow-up scan, again the five lesions with highest FDG uptake were chosen, which were not necessarily the same as in the baseline scan. To qualify as target lesion, a lesion had to have a minimal uptake of two times SUL of the background uptake. As the liver was frequently diseased, the aortic blood pool was used as reference for background activity in all patients.

For TLG, a tumor VOI was automatically determined with a threshold of minimally two times mean activity of selected reference tissue. For most metastases, aortic blood pool served as reference tissue. For bone metastases, normal bone was used as reference tissue and for liver metastases normal liver tissue was used as reference tissue. In case of ubiquitously diseased liver, aortic blood

pool served as reference. TLG then was calculated as: $\text{mean uptake of VOI} \times \text{volume of VOI}$. For the total TLG score, per patient the same lesions were followed over the subsequent scans, and the sum of up to five lesions were determined (sumTLG).

Changes in SUL during treatment were determined by the percentage change compared to the baseline measurement: (post-treatment SUL – baseline SUL/baseline SUL), expressed in percentages.

A qualitative judgment was performed independently by two nuclear medicine physicians who were blinded for clinical, radiological and histopathological information. Images were scored as progressive metabolic disease, stable metabolic disease, partial metabolic response, and complete metabolic response. After independent scoring, a consensus score was established.

Results

Patient categories: obese and elderly patients

Two patients were obese and elderly, and these patients were excluded in the analysis of pharmacokinetic differences between control, elderly, and obese patients. GM everolimus C_{trough} was 11.1, 15.9, and 17.1 µg/L, for control, obese, and elderly patients, respectively. The mean of the log-transformed C_{trough} differed between the three groups (one-way ANOVA: p=0.022). We performed two post-hoc tests, comparing elderly versus control patients and obese versus control patients. Elderly patients had a significantly higher mean log-transformed C_{trough} compared to control patients. However, in a multivariable linear regression analysis with age and BMI as covariates, both were not significantly associated with C_{trough}.

Control, obese, and elderly patients had a dose change event <3 months in 40%, 55%, and 78% of cases, respectively. The group of elderly patients had the shortest time to dose change event (41 days, compared to 141 days for control patients and undefined for obese patients, p=0.0053).

Specifically, patients >70 years had a significantly shorter time to a dose change event compared to patients <70 years: 42 versus 141 days (p=0.0019, HR 0.17, 95% CI 0.05 – 0.52). In a multivariable Cox regression analysis with age and BMI as covariates, both were not significantly associated with the time to a dose change event. Median PFS was not significantly different for control, obese, and elderly patients (log rank, p=0.10).

References

1. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-65.