Effect of moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib

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Erythromycin significantly increase the pharmacokinetic exposure of palbociclib

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20410

Source
Nationaal Trial Register

Brief title
M18CYP

Health condition

Breast cancer patients treated with palbociclib

Sponsors and support

Primary sponsor: NKI-AVL
Source(s) of monetary or material Support: None

Intervention

Outcome measures

Primary outcome

The primary objective of this trial is to study the effect of the moderate CYP3A4 inhibitor

erythromycin on the pharmacokinetics of palbociclib, measured as AUC0-24h, Cmax and Cmin.

Secondary outcome

The secondary objective of this trial is to compare the incidence and severity of adverse events with (a week) and without co-administration of the moderate CYP3A4 inhibitor erythromycin, according to CTC-AE v5.0.

Study description

Background summary

Palbociclib is an inhibitor of cyclin-dependent kinase 4 (CDK4) and CDK6, indicated for the treatment of hormone receptor positive, Her2 negative, locally advanced or metastatic breast cancer. Palbociclib exposure has been linked to toxicity, with a higher area under the concentration-time curve (AUC) being associated with a greater reduction in absolute neutrophil count. Common adverse reactions reported in patients receiving palbociclib are also fatigue, nausea, stomatitis and diarrhoea (≥20%), which can seriously hamper quality of life. Palbociclib is metabolized by CYP3A4 and its exposure was significantly increased when co-administered with itraconazole (a strong CYP3A4 inhibitor), resulting in an increase in AUC0-inf and Cmax of 87% and 34%, respectively. Therefore, it is advised to avoid concomitant use of strong CYP3A4 inhibitors. If co-administration with a strong CYP3A4 inhibitor cannot be avoided, the daily palbociclib dose should be reduced to 75 mg (60% of standard dose). Although it is recommended by the FDA to evaluate the impact of moderate inhibitors in the case of clinically significant interactions with strong inhibitors, no management guidelines for concomitant use of palbociclib with moderate CYP3A4 inhibitors have been reported.[2] Yu et al published an physiologically based pharmacokinetic (PBPK) model, in which they simulated the effect of the moderate CYP3A4 inhibitors verapamil and diltiazem. They reported an increase in AUC and Cmax of 38% and 22% for verapamil; and 42% and 23% for diltiazem, respectively. The authors conclude that the risk of drug-drug interactions for palbociclib co-administered with moderate CYP3A4 inhibitors is relatively modest and that no dose adjustment is needed. However, a 40% increase in exposure could be clinically relevant, since higher palbociclib exposure is associated with increased toxicity like fatigue, nausea, stomatitis and diarrhoea which can seriously hamper quality of life (not only lab abnormalities). Based on the above, we propose to conduct a randomized pharmacokinetic cross-over trial to study the effect of the moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib. This study will provide enough data to guide future physicians and patients on dosing instructions and adverse events expectations when in daily care palbociclib is given to patients using a moderate CYP3A4 inhibitor.

Study objective

Erythromycin significantly increase the pharmacokinetic exposure of palbociclib

Study design

Pharmacokinetic sampling will be performed at Day 7 and Day 21 of the study (palbociclib alone vs. palbociclib + erythromycin, sequence depending on randomization) at the following timepoints: predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours postdose.

Intervention

Patients will use erythromycin 500 mg TID during one week concomitant with palbociclib.

Contacts

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Eligibility criteria

Inclusion criteria

• Histological or cytological proof of cancer for which palbociclib is considered standard care; • Age ≥ 18 years; • WHO performance status of 0, 1 or 2; • Adequate organ function per judgement of the treating physician; • Able and willing to undergo blood sampling for PK analysis.

Exclusion criteria

• Concomitant use of medication(s) which could influence the pharmacokinetics of palbociclib within 14 days or five half-lives of the drug (whichever is shorter) before start of the study, consisting of (but not limited to) CYP3A4-inhibitors/inductors • Women who are pregnant or breast feeding; • Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study

compliance; • Palbociclib related side effects that would require a dose reduction per judgement of the treating physician; • QT duration corrected for heart rate > 450 ms or > 480 ms for subjects with bundle branch block.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-02-2019
Enrollment:	14
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	22-02-2019
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 45801
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7549
CCMO	NL67583.031.18
OMON	NL-OMON45801

Study results