Effect of moderate CYP3A4 inhibitor erythromycin on the pharmacokinetics of palbociclib

Gepubliceerd: 22-02-2019 Laatst bijgewerkt: 13-01-2025

Erythromycin significantly increase the pharmacokinetic exposure of palbociclib

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20410

Bron
Nationaal Trial Register

Verkorte titel
M18CYP

Aandoening

Breast cancer patients treated with palbociclib

Ondersteuning

Primaire sponsor: NKI-AVL
Overige ondersteuning: None

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

Erythromycin significantly increase the pharmacokinetic exposure of palbociclib

Onderzoeksopzet

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.

Onderzoeksproduct en/of interventie

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

Contactpersonen

Publiek

NKI-AVL
Steffie Groenland

020 512 6152

Wetenschappelijk

NKI-AVL
Steffie Groenland

020 512 6152

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

• 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

• 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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	22-02-2019
Aantal proefpersonen:	14
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	22-02-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 45801
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

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

Resultaten