Impact of potential drug-drug interactions on adherence to endocrine therapy (ET) among patients with breast cancer (BC) in the Health Improvement Network (THIN™)

Elie Rassy[1], Aurélie Bardet[2,3], Omar Bougacha[4], Laurene Gantzer[4], Béranger Lekens[4], Ines Vaz-Luis[1], Suzette Delaloge[1], Fabrice André[1], Stefan Michiels[2,3], Barbara Pistilli[1]

1. Department of Medical Oncology, Gustave Roussy, University Paris-Saclay, Villejuif, France; 2. Department of Biostatistics and Epidemiology, Gustave Roussy, University Paris-Saclay, Villejuif, France; 3. Oncostat U1018, Inserm, University Paris-Saclay, labeled Ligue Contre le Cancer, Villejuif, France; 4. CEGEDIM R&D, Boulogne-Billancourt Paris, France

Background

Non-adherence to adjuvant endocrine therapy (ET) remains a major issue in patients with hormone-receptor positive (HR+) breast cancer (BC) and negatively impacts the long-term recurrence and survival outcomes. Recently, we reported that 16.0% of premenopausal patients of the prosepective CANTO cohort had a serum tamoxifen level below the set adherence threshold and had an increased risk of breast cancer distant recurrences [1].

Polypharmacy and drug interactions are often overlooked although they can be encountered in 50-91% of patients with breast cancer and can be associated with medication nonadherence, and mortality among patients with cancer [2-4]. Thus identification of patients for whom polypharmacy constitutes a barrier to ET adherence may enable the implementation of personalized strategies.

Objectives

This study aimed to explore the potential drug-drug interactions (PDDI) between comedications and ET and investigate their association with adherence.

Patients and methods

Study design: This was a retrospective longitudinal study based on a subset of patients from the French version of The Health Improvement Network (THIN™) database. THIN™ is a real-world European database that collects medical records at the physician level and is coded according to the International Classification of Disease, 10th Revision (ICD-10) codes.

References:
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Eligibility: We included all women ages 18 years or older who had a diagnosis of any stage of invasive breast cancer at any stage (ICD10-code C50.x) and had completed or were receiving ET with either tamoxifen (Anatomical Therapeutic Chemical [ATC] class L02BA01) or an aromatase inhibitor (ATC classes L02BG.x; letrozole, anastrozole, exemestane) between 1994 and 2021. Eligible patients had to have at least one year of continuous enrollment and be followed by the general practitioner before and after the initiation of ET to ensure the completeness of the data.

Variables of interest: Demographic data (age), comorbidities, and ET category (tamoxifen or aromatase inhibitor), prescription and reimbursement data of the ET to assess switching of agents, complete discontinuation of agents, and medication possession ratio (MPR).

- MPR was used to evaluate adherence. According to standard definition, MPR was assessed as the proportion of a time period where a medication supply was available. In a given one-year period, MPR was calculated by dividing the duration of ET prescribed by the duration between two consecutive dispenses (5).
- Discontinuation of ET was defined as no dispensation in the following year or having an observed gap of 30 or more days between the end of the previous supply and the subsequent dispensing of ET.
- According to prior data, MPR ≥ 0.80 defined adherence to therapy among patients who received at least one ET prescription and included nonadherent patients during the previous interval or switchers to other ET (6).

Medication use at baseline and during subsequent years of treatment with ET was retrieved from the pharmacy dispensing data. The PDDI with the medication classes was limited to the year of the prescription and did not carry forward to subsequent years of ET unless the prescription was renewed. PDDI between daily medication and ET were analyzed using the Claude Bernard Drug Database and categorized into absent, minor (combination to take into account), moderate (combination requiring precautions for use), major (combination not recommended) and contraindicated.

Statistical analysis: The multivariable analysis was adjusted for age, baseline comorbidities, PDDI (the worst interaction was retained for the model), and adherence during the previous year. All tests were two-sided and a p-value < 0.05 was considered statistically significant

Ethical approval: THIN™ comprises fully anonymized electronic medical records compliant with the European general data protection regulations (GDPR). The database obtained approval from the French National Data Protection Authority (CNIL) for data collection in 2002.

Results

The database includes 47,250 patients with breast cancer among whom 19 992 patients received ET during their cancer care. Among the eligible patients, only those with a minimum follow-up of one year were analyzed. Thus 10,863 participants were considered for this study. The majority of participants was aged 50 years and above (n = 9,131; 84.1%) and a minority was younger than 30 years of age (n = 14; 0.1%). At baseline, PDDI was identified in 391 patients (11.0%) of the tamoxifen cohort and 454 patients (5.7%) in the aromatase inhibitor cohort.

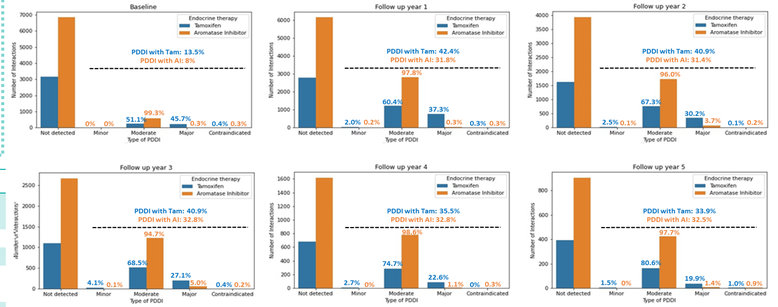
Characteristics of the patients with BC undergoing ET

		Tam cohort (n=3,564)	AI cohort (n=7,299)
Age categories	< 30 years	11 (0.3%)	3 (0.04%)
	30-39 years	234 (6.6%)	23 (0.3%)
	40-49 years	1,264 (35.5%)	196 (2.7%)
	50-59 years	1,133 (31.8%)	1,480 (20.3%)
	60-69 years	408 (11.4%)	2,601 (35.6%)
	≥ 70 years	514 (14.4%)	2,995 (41.0%)
Comorbidities	CAD	12 (0.3%)	53 (0.7%)
	HTN	950 (26.7%)	3,708 (50.8%)
	DM	193 (5.4%)	1,008 (13.8%)
	Dysthyroidism	16 (0.4%)	42 (0.6%)
	RD	57 (1.6%)	225 (3.1%)
	Osteoarthritis	454 (12.7%)	1,883 (25.8%)
	Epilepsy	35 (1.0%)	98 (1.3%)
	Dementia	5 (0.1%)	18 (0.2%)
	CVD	112 (3.1%)	393 (5.4%)
	COPD	46 (1.3%)	190 (2.6%)
	Asthma	370 (10.4%)	916 (12.5%)
	Depression	1,076 (30.2%)	2,264 (31.0%)

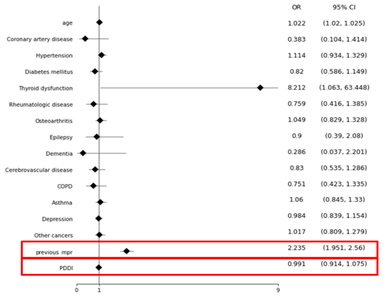
CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CVD: cerebrovascular disease; DM: diabetes mellitus; HTN: hypertension; RD: rheumatoid disease

After a median follow up of 1015 days, the absolute number of patients undergoing ET decreased from year 1 to year 5. Among the patients receiving ET, the adherence per year increased from 79.3% and 88.8% at year 1 to 89.5% and 92.8% at year 5, for tamoxifen and aromatase-inhibitors respectively. Among the patients that switched therapy, almost two-thirds of the switch occurred during year 1 (63.6% and 60.5% in the tamoxifen and aromatase inhibitors respectively). This proportion decreased steadily over the study period to 2.6% and 1.5%, in the two cohorts.

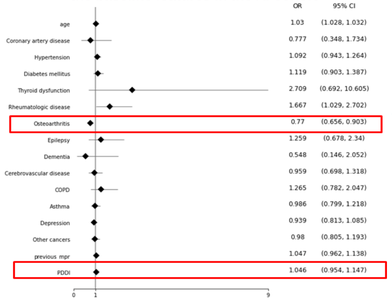
No association between adherence and PDDI was found neither in the tamoxifen (OR 0.99, 95% CI 0.91-1.08) nor aromatase inhibitor (OR 1.05, 95% CI 0.95-1.15) cohorts. There were no statistically significant differences between the different PDDI categories in comparison to no PDDI. In the tamoxifen cohort, higher odds of adherence were observed among adherent patients during the previous year (OR 2.24, 95% CI 1.95-2.56). In the aromatase inhibitor cohort, lower odds of adherence were observed among patients with osteoarthritis (OR = 0.77, 95% CI 0.66-0.9).



Forest plot showing the association between MPR and the baseline features in the tamoxifen cohort



Forest plot showing the association between MPR and the baseline features in the AI cohort



Study limitations

Due to the inherent limitations of registry analysis, such as missing data and exhaustiveness of the data, these results should be interpreted carefully. The medication possession ratio may be a suboptimal method for measuring adherence but is the most commonly used and reproducible parameter when adherence is assessed through administrative pharmacy dispensing data,

Conclusions

This study provided important insights concerning the prevalence of PDDI, the considerable proportion of PDDI (mainly moderate and major) that seemed to increase from baseline onwards, and the limited impact of PDDI on adherence. Notably, the contraindicated PDDI were < 1%.

These findings highlight the importance of a comprehensive medication evaluation during each patient visit.

Although this study did not evaluate the impact of PDDI on breast cancer outcomes, which remain a controversial topic in the published literature, PDDI should be evaluated to avoid deleterious interactions.

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Presenter: Elie Rassy MD MSc MPH
Conflicts of interest: None