Child outcomes after prenatal exposure to platinum and taxane-based chemotherapy: an unplanned interim analysis of the international network on cancer, infertility, and pregnancy study

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Summary

Background Platina and taxanes are frequently used chemotherapeutic agents to treat cancer, also when diagnosed during pregnancy. This report presents an interim analysis of the largest series of children prenatally exposed to platinum and/or taxane agents and aims to determine their physical health and neurocognitive outcomes.

Methods As part of a multicentre, prospective cohort study (ClinicalTrials.gov: NCT00330447), children born between 2000 and 2022 were assessed between 2005 and 2024 at ages 1.5–18 years (interim analysis; median length of follow-up, 3.2 years (IQR 3.0–6.4)) by a comprehensive neurocognitive test battery, parent-reported questionnaires, and a physical assessment. Mixed-effects regression and Type III Analysis of Variance models were used to investigate associations between these outcomes and platinum/taxane cumulative dose and agent type, with best-fit models corrected for age and covariates (gestational age at birth, chemotherapy timing, other chemotherapy, sex, parental education level, maternal death).

Findings In total, 144 children were included (13% exposed to platinum, 62% to taxanes, 25% to both). Of these, 101 were assessed at age 1.5 years, 96 at age 3, 63 at age 6, 32 at age 9, 18 at age 12, 7 at age 15, and 2 at age 18 years. Neurocognitive outcomes were within normal ranges across all ages, compared with test-specific normative data. Eight children (6%) reported ototoxicity, seven (5%) reported chronic medical conditions, three (2%) had congenital malformations, and two (1%) were diagnosed with Attention-Deficit Hyperactivity Disorder. Thirty-three children (23%) needed extra neurocognitive support, of which 64% were born preterm. Children prenatally

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exposed to paclitaxel scored lower on visuospatial (β = 0.64 ± 0.21, p = 0.0052) and verbal memory (β = 0.68 ± 0.27, p = 0.015) than those exposed to docetaxel.

Interpretation In this interim analysis, we found normal neurocognitive outcomes and no increase in congenital malformations nor medical conditions after prenatal exposure to platinum/taxane-based chemotherapy. However, owed to the limited number of older children, further investigation regarding their potential neurotoxicity and its long term effects is necessary in follow-up studies with larger samples.

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Keywords: Cancer during pregnancy; Prenatal chemotherapy exposure; Platinum-based chemotherapy; Taxane-based chemotherapy; Child development

Research in context

Evidence before this study

We searched PubMed for all article types from database inception to 29 April 2024, with the search terms ((pregnancy) OR (prenatal)) AND ((platinum) OR (platin) OR (cisplatin) OR (carboplatin) OR (oxaliplatin) OR (taxane) OR (taxol) OR (paclitaxel) OR (docetaxel)), without restricting the search to a particular language. Several case series exist that summarise the multiple smaller case reports, although follow-up duration is limited to a median range of 10–33 months, and neurocognitive outcome measures are often limited to parent self-report or single-measure developmental testing. There is still uncertainty about the possible foetal toxicity and risk for impaired child development if these agents are administered during pregnancy, especially considering that neurotoxicity is well-acknowledged for both taxanes and platina.

Added value of this study

This multicentre, prospective cohort study by the International Network on Cancer, Infertility, and Pregnancy (INCIP) represents an interim analysis of the largest series of children born from mothers treated with platinum- and/or taxane-based chemotherapy during pregnancy. Children were followed-up prospectively from birth at the intervals of 1.5, 3, 6, 9, 12, 15, and 18 years (median last age at follow-up, 3.2 years (IQR 3.0–6.4); median number of assessments, 2 (IQR 1–3)), for the holistic and standardised assessment of neurocognitive, psychosocial, and physical health outcomes. Our study provides preliminary findings suggesting normal neurocognitive outcomes, with no observed increase in congenital malformations or chronic health problems; however, no definite conclusions can be drawn at this stage.

Implications of all the available evidence

Previous research on cancer treatment during pregnancy has focussed on child outcomes of heterogeneous groups exposed to different (combinations of) cancer treatments and chemotherapeutic agents during pregnancy. The heterogeneity of the data reduces its clinical usability, which the current manuscript aimed to address. While our preliminary findings contribute to the ongoing discussion and may inform clinical decision-making, further research is necessary to confirm these results and to support the development of clinical guidelines regarding chemotherapy during pregnancy.

Introduction

Cancer is estimated to be diagnosed in 1 in 1000 pregnancies. Platinum- and taxane-based chemotherapeutic agents are widely used to treat gynaecological and breast cancers, which account for about 60%–75% of cancer types diagnosed during pregnancy.[1,2] The incidence of cancer during pregnancy is rising as women tend to delay childbearing and improved prenatal cell-free DNA testing and ultrasound facilitate pre-symptomatic cancer detection.[3,4] The combination of platinum- and taxane-based agents improves maternal survival in breast and gynaecological cancers compared with single-agent platinum or taxane regimens, and is better tolerated than taxane–anthracycline combinations.[5,6]

Platinum compounds show a high transplacental transfer (range 4.0–57.5%), and can thus readily reach the foetus.[7–10] Moreover, since platinum agents cause direct DNA damage, they might affect placental and foetal cells directly.[1] During pregnancy, mainly cisplatin and carboplatin are used, whereas fewer indications exist for oxaliplatin.[7] Cisplatin is related to higher neurotoxicity, ototoxicity, and hematopoietic suppression compared to carboplatin.[11,12]

In contrast to platinum, the transplacental transfer measured in blood is low for both paclitaxel and docetaxel (range 1.5–7.0%).[7,13,14] Taxanes are known substrates for P-glycoprotein, a placental transporter that limits transfer to the foetus.[15] Nevertheless, levels of

paclitaxel and its metabolites found in the meconium of newborns confirm human foetal exposure, with foetal tissues containing about 15.0% of the maternal level.[16] Taxanes are highly tissue-bound, which facilitates their storage in foetal tissue and increases their exposure time to the foetus.[8]

Both platinum and taxane compounds carry moderate to high risks for adverse neonatal outcomes. Specifically, platinum-based chemotherapy is linked to a threefold increase in the risk of infants being small for gestational age. Taxane chemotherapy is associated with more than double the risk of neonatal intensive care unit admissions, largely due to prematurity, and nearly a quarter of neonates are born small for gestational age.[1,17]

Furthermore, prenatal exposure to platinum, especially cisplatin, may be associated with ototoxicity.[18] In childhood cancer patients, platinum exposure increased the risk for long-term sensory impairment[19,20] and neuromuscular dysfunction[21] due to direct irreversibly toxicity. Taxane exposure, especially paclitaxel, has been linked to peripheral neuropathy in children.[22] Furthermore, studies on long-term outcomes of (childhood) cancer patients treated with various chemotherapeutic agents show an increased risk for long-term cognitive impairment, particularly in processing speed and memory.[23,24] While standardised studies on child outcomes after cancer and chemotherapy during pregnancy show overall reassuring results, these studies also pooled children exposed to different chemotherapeutic agents.[25–27]

Evidence is lacking on the specific impact of platinum- and taxane-based chemotherapy during pregnancy on the long-term outcomes of the child. Given that these agent types can more readily reach or be exposed for longer to the foetus, are potentially more neurotoxic, and are associated with adverse neonatal outcomes, further research is necessary to understand their effects on the long-term development of children. Therefore, this prospective cohort study of the International Network on Cancer, Infertility, and Pregnancy (INCIP) aims to describe the physical health, neurocognitive, and psychosocial outcomes throughout childhood of children prenatally exposed to platinum- and/or taxane-based chemotherapy.

Methods

Study design and participants

In this multicentre, prospective cohort study, children of mothers treated with platinum-based or taxane-based chemotherapy, or a combination of both, during pregnancy, were identified from the Child Follow-up INCIP registry (voluntary registration), enrolled prospectively, and assessed using age-adapted standardised neurocognitive test batteries, parent-reported questionnaires, and a health examination.

Cases were excluded if they did not result in a live birth or if no consent was given to participate in the child follow-up study. In total, 181 maternal cases of platinum- and/or taxane-based chemotherapy treatment during pregnancy were registered. Of these, 7 cases (4%) did not result in a live birth: 2 terminations of pregnancy (1%), 2 miscarriages (1%), 3 stillbirths (2%). One child (1%) died the day after delivery due to a prematurity-related cerebral haemorrhage. For 29 (16%) live-born children, no parental consent was given to participate.

Live-born children with parental consent to participate were enrolled prospectively from birth and assessed at pre-defined ages (1.5, 3, 6, 9, 12, 15, 18 years), as previously described.[28] Children were born between May 2000 and March 2022, and assessed at six centres: Princess Máxima Center for Pediatric Oncology (Netherlands), University Hospitals Leuven (Belgium), Cooper University Health Care (United States of America), Fondazione IRCSS San Gerardo (Italy), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Italy), and University Hospital Kralovske Vinohrady (Czechia).

This study represents an interim analysis of our cohort. Figure S1 (Supplement) depicts an overview of the recruitment and age distribution. As many children have not yet reached the older age brackets, the current follow-up outcomes reflect the age distribution of the cohort at this stage.

Ethics

The University Hospitals of Leuven (UZ Leuven) represents the coordinator and sponsor of this multicentre study. Ethical approval was obtained by the Ethical Committee of UZ/KU Leuven (reference number B322201420048), as well as of the local ethics committee of each participating centre. Written informed consent was acquired from the parents of all participating children at each timepoint. Written informed assent was additionally acquired from the children from age 12 years, and written informed consent at age 18 years. The study is registered with ClinicalTrials.gov (NCT00330447). This analysis represents a non-preplanned analysis of the protocol.

Outcomes

The neurocognitive examination was conducted by a trained psychologist. The protocol used validated age- and language-specific assessments of early cognitive development, intelligence, attentional functioning, memory, behavioural manifestation of executive functioning, and psychosocial functioning.

Early cognitive development was assessed using the Bayley Scales of Infant Development (BSID[29]) at age 1.5 and 3 years, and Intelligence (IQ) using age-appropriate versions of the Wechsler Intelligence Scale (WPPSI,[30] WISC,[31] WAIS[32]) from age 6 to 18 years. Attentional

functioning was assessed from age 6 to 18 years using the Amsterdam Neuropsychological Tasks (ANT[33]). Memory (visuospatial and verbal) was assessed from age 6 to 18 years using the Children's Memory Scale (CMS[34]) and Auditory Verbal Learning Test (AVLT[35]).

Executive functioning behaviours and psychosocial functioning were assessed separately using, respectively, the following parent-report questionnaires: Behavior Rating Inventory of Executive Function (BRIEF[36,37]) from age 3 to 18 years, and the Child Behavior Checklist (CBCL[38]) from age 1.5 to 18 years.

Physical health was assessed using a general paediatric and neurological examination by a paediatric neurologist, and parents completed a general health questionnaire at each timepoint.

Exposure to platinum- and/or taxane-based chemotherapy was ascertained from the INCIP registry. This included detailed information on the specific platinum (cisplatin, carboplatin, oxaliplatin) and taxane (paclitaxel, docetaxel) compounds used, the gestational age at the start and end of exposure (recorded in weeks), the total number of chemotherapy cycles administered during pregnancy, and the dose per cycle (reported in mg/m^2, after conversion from AUC for carboplatin). Additionally, exposure to other treatments, such as different chemotherapy regimens, surgery, and radiotherapy, was also collected from the INCIP registry. For other chemotherapy treatments, details included agent type(s) and the gestational age at the start and end of exposure, recorded in weeks.

Additional data collected from the INCIP registry included obstetrical information such as the gestational age at birth, the biological sex of the neonate, and any congenital malformations. Parental information gathered included the education levels of both parents and the mother's status at the latest follow-up.

Statistics

Raw scores from the neurocognitive test battery and parent-reported questionnaires were converted into standardised scores using test-specific normative data based on a normal distribution (bell curve), as specified in the respective scoring manuals (adjusted for age, country or language, and if available, sex), enabling comparison with the general population. To ensure comparability across different outcomes, standardised scores were subsequently converted to z-scores, with a mean of 0 and a standard deviation of 1.[39] In the context of z-scores, it is generally accepted that scores within one standard deviation of the mean (i.e. between a z-score of −1 and 1) are considered within the "normal range". This encompasses approximately 68% of the population under a normal distribution, with 16% of the general population scoring below a z-score of −1, or one standard deviation below the mean. See Table S1 (Supplement) for an overview of the population norms per test and the instructions for converting between z-score and actual standard t-score. For the ANT, BRIEF, and CBCL, standardised z-scores were inverted so that higher scores signify a better performance.

For each neurocognitive outcome, a composite score was created by taking the 'total score' of a test, if available (BSID, WPPSI, WISC, WAIS, BRIEF, CBCL), or by averaging the scores from all subtests within each test (ANT, CMS, AVLT).

Mean scores per neurocognitive outcome at each timepoint were determined for each chemotherapy group (platinum only, taxane only, both), and compared using Kruskal–Wallis tests using a significance level of $\alpha = 0.05$.

Cumulative dose and agent type were investigated separately as independent factors in linear mixed-effects regression models for each neurocognitive outcome. Age was included as a covariate in all models, with participant as a random intercept to account for repeated measures. Neurocognitive outcomes were treated as continuous dependent variables. Other covariates were fitted and best-fit models were selected based on Bayesian Information Criterion (BIC). Subsequently, Type III Analysis of Variance (ANOVA) models with Satterthwaite's method were applied to assess the significance of the modelled effects. Satterthwaite's method is a robust approach for calculating degrees of freedom in ANOVA when sample sizes are unequal or variances not homogeneous. Due to the small sample sizes and the need to prevent false-negative findings, Bonferroni's correction was applied only within each outcome and exposure group (i.e. per two analyses; $\alpha = 0.025$), in line with the discussion by RJ Feise (2002).[40]

Cumulative dose was calculated by summing the dose administered during each chemotherapy cycle, per platinum and taxane agent. Doses for cisplatin, oxaliplatin, paclitaxel, and docetaxel were added as given, in mg/m^2. To compare doses of platinum agents, the dose for carboplatin was first adjusted to an equivalent dose in mg/m^2, due to the differential dosing of carboplatin according to "area under the curve" based on renal function (glomerular filtration rate). This adjustment converted the administered dose of carboplatin to the dose corrected for body surface area (in mg/m^2) and dividing this by 4, according to the general clinical consensus that a ratio of 4:1 is used between carboplatin and cisplatin.[41]

Agent type was divided into the general categories of platinum (-based) chemotherapy, taxane (-based) chemotherapy, or both. For platina, agent type was further divided into the categories of carboplatin and cisplatin. For taxanes, agent type was divided into paclitaxel and docetaxel. Oxaliplatin and combinations of specific platinum or taxane agents were excluded from inferential analyses due to small sample sizes (all ≤ 3).

The following covariates were considered: sex (female/male), gestational age at birth (weeks), gestational

age at start platinum/taxane chemotherapy (weeks), gestational age at start any chemotherapy (weeks), other chemotherapy (yes/no), period between last chemotherapy cycle and delivery (days), maternal death (yes/no and before child age 2 years/after 2 years/no), maternal and paternal education (primary or secondary education/Bachelor diploma/Master diploma or beyond), country (Netherlands/Belgium/USA/Italy/Czechia), and language (Dutch/French/English/Italian/Czech).

Missing data at specific timepoints was assumed to be missing at random, since only 4 children (<3%) were permanently lost to follow-up, and handled using Maximum Likelihood Estimation. Data at 15 and 18 years were excluded from all models due to low sample sizes (<10). Children with missing data for parental education were excluded from analyses that included these covariates, in a complete-case manner. No data was missing for platinum/taxane chemotherapy factors, or other covariates.

Role of funding source

The funders of the study were not involved in the study design, data collection, data analyses, interpretation, writing or editing of the article, or decision to submit for publication.

Results

A total of 144 children were included, of which 5 twin pairs. The median length of follow-up from birth was 3.2 years (IQR 3.0–6.4 years) and the median number of assessments was 2 (IQR 1–3). Platinum- and/or taxane-based chemotherapy was administered at a median of 27 (IQR 22.0–30.0) to 34 weeks (IQR 30.5–35.0) of gestation. Table 1 gives an overview on demographic and treatment characteristics. Table 2 gives an overview of sample size per neurocognitive outcome and age, across agent type groups (platinum, taxane, both).

In our cohort, 83 children (/144, 58%) were born **preterm**. Of these, 4 (/144, 3%) were born extremely preterm (<28 weeks of gestation), 11 (8%) very preterm (28 to less than 32 weeks), 15 (10%) moderately preterm (32 to less than 34 weeks), and 53 (37%) late preterm (34 to less than 37 weeks).

Three children (/144, 2%) had **congenital malformations**, including syndactyly and clinodactyly, congenital penile curvature, and thyroglossal duct cyst, respectively. Of these children, one was exposed to six cycles of docetaxel, doxorubicin, and cyclophosphamide (3-weekly) in the first 18 weeks of gestation, as the pregnancy was unknown at time of treatment. The remaining two children were exposed to paclitaxel or docetaxel, in combination with both doxorubicin and cyclophosphamide, in the second and third trimesters.

Seven children (/144, 5%) had **medical conditions**, leading to chronic problems: mitral valve stenosis, hip dysplasia, celiac disease, immunosuppression, epilepsy,

Demographic characteristic	Children (N = 144[a])	
	N	%
Sex[b]		
Female	75	52
Male	69	48
Country		
The Netherlands	61	42
Belgium	38	26
The United States of America	28	19
Italy	13	9
Czechia	4	3
Highest level of parental education		
Mother		
Primary or secondary school	40	29
Bachelor's degree	48	35
Master's degree or beyond	28	20
Unknown	23	16
Father		
Primary or secondary school	44	32
Bachelor's degree	41	29
Master's degree or beyond	26	19
Unknown	28	20
Mother status during childhood		
Not deceased	113	81
Deceased	26	19
	Median	IQR
Age child at maternal death (N = 26)—months	11.8	8.2–24.4
Gestational age at birth—weeks	36.7	34.6–37.7
Treatment characteristic	**Mothers (N = 139)**	
	N	%
Cancer type		
Breast	91	66
Cervical	32	23
Ovarian	6	4
Gastrointestinal	4	3
Oropharyngeal	2	1
Lung	2	1
Vaginal	1	1
Sarcoma	1	1
Cancer treatment during pregnancy		
Chemotherapy alone	59	42
Chemotherapy + Surgery	74	53
Chemotherapy + Radiotherapy	2	1
Chemotherapy + Surgery + Radiotherapy	4	3
Platinum/taxane chemotherapy		
Platinum only	18	13
Cisplatin	13	72
Oxaliplatin	3	17
Carboplatin	2	11
Taxane only	86	62
Paclitaxel	62	72
Docetaxel	21	24
Paclitaxel + docetaxel	3	4

(Table 1 continues on next page)

Treatment characteristic	Mothers (N = 139)	
	N	%
(Continued from previous page)		
Platinum and taxane	35	25
Carboplatin + paclitaxel	28	80
Cisplatin + paclitaxel	5	14
Carboplatin + cisplatin + paclitaxel	1	3
Carboplatin + oxaliplatin + paclitaxel	1	3
Other chemotherapy		
AC	47	34
EC	19	14
FEC	19	14
FAC	2	1
Adriamycin	1	1
Cyclophosphamide	1	1
No other CT	50	36
	Median	IQR
Total platinum/taxane dose—mg/m^2	480.0	240.0–717.9
Platinum	315.0	210.0–422.0
Carboplatin (adjusted)	324.3	231.9–486.0
Cisplatin	240.0	200.0–300.0
Oxaliplatin	370.0	297.5–448.8
Taxane	400.0	240.0–678.0
Paclitaxel	480.0	300.0–700.0
Docetaxel	225.0	100.0–300.0
Gestational age at start platinum/taxane CT—weeks	27.0	22.0–30.0
Gestational age at end platinum/taxane CT—weeks	34.0	30.5–35.0
Gestational age at start any CT-weeks	19.0	16.0–23.0
Time between last CT cycle and delivery—days	18.0	8.5–29.0

Abbreviations: SD, Standard Deviation; AC, Adriamycin (Doxorubicin) and Cyclophosphamide; EC, Epirubicin and Cyclophosphamide; FEC, Fluorouracil, Epirubicin, and Cyclophosphamide; FAC, Fluorouracil, Adriamycin (Doxorubicin), and Cyclophosphamide; CT, Chemotherapy. [a]Including five twin pairs, which were counted only once for all characteristics except Sex and Country. [b]Ascertained by biological factors at birth.

Table 1: **Demographic and treatment characteristics of participants.**

Wolff-Parkinson-White syndrome, and KCNQ2-related early infantile epileptic encephalopathy (EIEE) with retinopathy of prematurity (retinal detachment), respectively. Two children (1%) were diagnosed with Attention-Deficit/Hyperactivity Disorder (at 6 and 9 years of age). Of these nine children, five were exposed to paclitaxel only, three to docetaxel only, and one to paclitaxel and cisplatin.

Eight children (/144, 6%) had **hearing loss or auditory processing impairment** (ototoxicity), based on parent-reports of abnormal auditory testing. Of these, six were prenatally exposed to platinum (11% of total platinum group) and five were born preterm (four late preterm, one very preterm). Five were prenatally exposed to cisplatin (of which four with paclitaxel and one switched to carboplatin after four cycles due to maternal intolerance), two to carboplatin (both with paclitaxel and one after switch from cisplatin), one to paclitaxel only, and one to docetaxel only. All prenatal cisplatin doses in this group were higher than the cohort median (240 mg/m^2).

Thirty-three children (/144, 23%) require(d) **extra neurocognitive support**: speech therapy (21), physical therapy (10), support at school (6), psychological therapy (6), and occupational therapy (2). Need for support was not associated with chemotherapy factors (cumulative dose, agent type, gestational age at start), but it was related to gestational age at birth ($\beta = -1.31 \pm 0.55$, $p = 0.018$). Twenty-one (64%) of these children were born preterm, of which two extremely preterm, six very preterm, and thirteen late preterm.

The **neurocognitive assessment** for the child with EIEE and retinal detachment **could not be performed** due to severe intellectual disability and visual impairment. This child (male) was prenatally exposed to cisplatin (420 mg/m^2) and paclitaxel (420 mg/m^2) between 17 and 23 weeks of gestation, and was delivered at 29 weeks of gestation with an elective caesarean section due to the deteriorating condition of the mother (cervical cancer). Additionally, this child suffered a severe rotavirus infection shortly after birth.

On average, group-wide **neurocognitive outcomes** were within normal ranges (z-score –1 to 1) at all ages, as compared with test-specific norms of the general population (Table 2). Intraclass correlation coefficients show stability over time for each test. When taking the average of all available scores over time, the percentage of children scoring below one standard deviation per outcome is within the expected range according to a normal distribution of the population (early cognitive development: 8%; intelligence: 8%, attention: 6%, visuospatial memory: 12%; verbal memory: 16%; executive function: 13%; psychosocial function: 9%). The child with EIEE was included across all outcomes as assumed to score lower than one standard deviation.

Children prenatally exposed to taxane agents were on average born later than those exposed to platinum agents ($\beta = 1.82$ gestational weeks ±1.59, $p = 0.020$) or a combination of taxane and platinum agents ($\beta = 1.37$ weeks ± 1.23, $p = 0.024$). No differences were found in **gestational age at birth** between cisplatin and carboplatin nor between paclitaxel and docetaxel ($p > 0.05$). Furthermore, no associations were found between cumulative dose and gestational age at birth. Gestational age at birth correlated with early cognitive development ($\beta = 0.061 \pm 0.026$, $p = 0.020$), but not with other outcomes.

Maternal death was negatively associated with attention ($\beta = -0.36 \pm 0.14$, $p = 0.011$), although no association was found between maternal death and agent type nor cumulative dose. **Maternal and paternal education level** were associated with early cognitive development ($\beta = 0.60 \pm 0.12$, $p < 0.0001$; $\beta = 0.54 \pm 0.12$, $p < 0.0001$) and intelligence ($\beta = 0.64 \pm 0.21$, $p = 0.004$; $\beta = 0.53 \pm 0.22$, $p = 0.020$). Parental education levels

Neurocognitive outcome	Age (Years)																				
	1.5			3			6			9			12			15			18		
	N	M (SD)	p	N	M (SD)	p	N	M (SD)	p	N	M (SD)	p	N	M (SD)	p	N	M (SD)	p	N	M (SD)	p
Early cognitive development			0.15			0.66															
Platinum	10	−0.61 (0.99)		9	0.04 (0.83)																
Taxane	59	−0.01 (0.91)		49	0.28 (0.76)																
Both	27	−0.18 (0.74)		24	0.36 (0.78)																
Intelligence									0.74			0.73			0.31			0.81			NA
Platinum							13	0.14 (1.09)		11	−0.17 (0.96)		5	−0.23 (1.14)		5	0.12 (1.23)		2	0.37 (0.14)	
Taxane							30	0.34 (0.94)		14	0.19 (0.86)		9	0.08 (0.99)		1	0.27 (NA)		0	NA	
Both							15	0.42 (1.08)		6	0.09 (0.83)		2	−0.90 (0.24)		1	−0.60 (NA)		0	NA	
Attention									0.84			0.20			0.30			0.88			NA
Platinum							10	0.04 (0.34)		8	−0.02 (0.56)		5	0.09 (0.56)		5	−0.48 (1.06)		2	0.07 (0.30)	
Taxane							25	0.08 (0.44)		14	−0.04 (0.41)		8	−0.00 (0.39)		1	−0.31 (NA)		0	NA	
Both							14	−0.02 (0.58)		6	−0.35 (0.36)		2	−0.47 (0.22)		1	−0.38 (NA)		0	NA	
Visuospatial memory									0.14			0.97			0.94			0.19			
Platinum							11	−0.23 (1.08)		8	0.37 (0.81)		5	0.43 (0.53)		5	−0.38 (0.84)				
Taxane							28	−0.02 (0.83)		15	0.48 (0.67)		8	0.40 (0.57)		1	0.67 (NA)				
Both							15	−0.52 (0.82)		6	0.29 (0.82)		2	0.13 (1.12)		1	−1.67 (NA)				
Verbal memory									0.51			0.19			0.22			0.24			NA
Platinum							11	−0.41 (0.90)		8	−0.01 (1.62)		5	1.29 (2.11)		5	1.20 (1.26)		2	1.04 (0.87)	
Taxane							27	−0.08 (0.63)		14	0.73 (1.06)		8	1.53 (1.14)		1	−0.21 (NA)		0	NA	
Both							15	−0.20 (0.88)		6	−0.16 (1.20)		2	−0.83 (1.18)		1	−1.75 (NA)		0	NA	
Executive function						0.64			0.14			0.44			0.42			0.27			NA
Platinum				4	0.55 (0.96)		7	0.30 (0.95)		7	−0.11 (1.27)		5	−0.40 (0.46)		5	−0.24 (0.80)		2	0.10 (1.13)	
Taxane				34	−0.01 (1.09)		27	0.07 (1.20)		14	−0.08 (1.16)		8	−0.28 (1.12)		1	0.50 (NA)		0	NA	
Both				21	0.00 (1.18)		15	0.63 (1.19)		5	0.66 (0.79)		2	0.25 (0.07)		1	0.50 (NA)		0	NA	
Psychosocial function			0.07			0.30			0.29			0.94			0.27			0.88			NA
Platinum	3	0.40 (1.14)		3	−0.10 (2.00)		10	−0.25 (1.03)		9	−0.37 (0.84)		5	−0.66 (0.78)		5	0.06 (0.89)		2	−0.05 (1.48)	
Taxane	49	0.48 (0.88)		51	0.27 (1.02)		34	−0.34 (0.98)		15	−0.23 (1.26)		10	0.24 (1.14)		1	0.20 (NA)		0	NA	
Both	22	1.03 (0.87)		21	−0.07 (0.86)		15	0.15 (0.66)		5	−0.16 (0.69)		2	−0.20 (0.00)		1	0.50 (NA)		0	NA	

Higher scores signify better performance across all outcomes. Abbreviations: N, sample size; M, mean; SD, standard deviation; p, p-value from Kruskal–Wallis test ($\alpha < 0.05$); NA, not applicable. [a]Instructions for converting between z-score and actual standard t-score can be found in Table S1 (Supplement). The t-scores for outcomes presented in this table can be found in Table S2 (Supplement).

Table 2: **Overview of neurocognitive outcome standardized z-scores[a] (norm-referenced mean of 0 and standard deviation of 1) per age group.**

were also not associated with platinum/taxane chemotherapy factors.

No differences in neurocognitive outcomes were found **cross-sectionally** between platinum, taxane, and platinum–taxane combination groups (Table 2), nor **longitudinally** (all $p > 0.05$). Fig. 1 depicts the trajectory of early cognitive development and intelligence per agent type.

When looking at the entire group of children, **no significant associations** were found for any **neurocognitive outcome** with **cumulative dose nor agent type** (platinum vs. taxane vs. both) (Table 3). These platinum/taxane factors also did not interact with time (all $p > 0.05$). When looking only at platinum-exposed children, no associations with platinum dose or agent type were found (Table 3). No associations were found with gestational age at start chemotherapy, nor period between last chemotherapy cycle and delivery (all $p > 0.05$).

When exploring only **taxane-exposed children**, **agent type** explained part of the variability in **visuospatial memory** ($p = 0.0052$) and **verbal memory** ($p = 0.015$) (Fig. 2). Children prenatally exposed to paclitaxel scored on average 0.64 z-score points (±0.21) lower on the standardized composite score of visuospatial memory and 0.68 z-score points (±0.27) lower on that of verbal memory compared to children prenatally exposed to docetaxel. A sensitivity analysis showed that the association with visuospatial memory remained significant in children exposed to single-agent taxane chemotherapy (exclusion of paclitaxel–carboplatin combination) ($\beta = -0.75 \pm 0.26$, $p = 0.0073$, $N = 26$), while the association with verbal memory was rendered insignificant ($\beta = -0.46 \pm 0.34$, $p = 0.18$, $N = 25$). In this sensitivity analysis, it is important to note the reduced sample size and hence power. No other associations with taxane factors were found (Table 3).

When considering only **non-adjusted models** (see Table S3), taxane agent type also explained **attention**, with paclitaxel-exposed children scoring on average 0.34 z-score points (±0.14) lower than docetaxel-exposed children. However, this association did not remain significant when adjusting for maternal death (Table 3), although prevalence of maternal death did not differ between paclitaxel- and docetaxel-exposed groups ($p > 0.05$). Furthermore, this association was rendered insignificant in a sensitivity analysis including only children exposed to single-agent taxane chemotherapy ($\beta = -0.39 \pm 0.17$, $p = 0.033$, $N = 23$).

Discussion

In this prospective, multicentre cohort study, we report on the interim analysis of the physical health, neurocognitive, and psychosocial outcomes of 144 children born to mothers who were treated with platinum- and/or taxane-based chemotherapy during pregnancy. Across childhood, all neurocognitive outcomes were on average within normal ranges, as compared with normative data of the general population. Only 5% of our cohort suffered from chronic physical health conditions and 2% from congenital malformations, which is in line with the global prevalence.[42] Of the latter, one

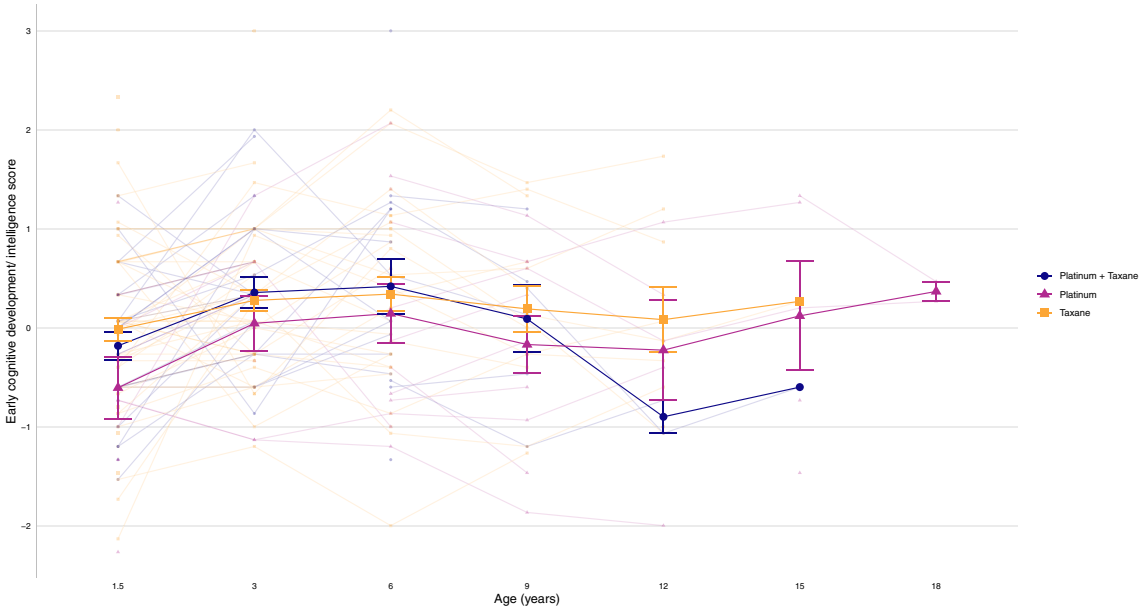

Fig. 1: Individual trajectories of standardised early cognitive development (1.5–3 years) and intelligence (6–18 years) by chemotherapy agent type, with bold lines signifying group averages. Sample size per age, per group (platinum + taxane, platinum only, taxane only; respectively): 1.5 years (27, 10, 59), 3 years (24, 9, 49), 6 years (15, 13, 30), 9 years (6, 11, 14), 12 years (2, 5, 9), 15 years (1, 5, 1), 18 years (0, 2, 0).

Fixed effect		Neurocognitive outcome																					
		Early cognitive development[a]			Intelligence[b]			Attention[c]			Visuospatial memory[d]			Verbal memory[d]			Executive functioning[d]			Psychosocial functioning[d]		
		N	F (df)	p	N	F (df)	p	N	F (df)	p	N	F (df)	p	N	F (df)	p	N	F (df)	p	N	F (df)	p
Group																							
Platinum/ Taxane	Dose (mg/m^2)	100	0.78 (1, 79)	0.38	55	0.08 (1, 50)	0.78	52	0.00 (1, 46)	1.00	57	0.01 (1, 54)	0.93	56	1.46 (1, 62)	0.23	89	3.89 (1, 83)	0.05	131	2.21 (1, 119)	0.14
	Agent (*Platinum, taxane, Both*)	100	1.43 (2, 80)	0.24	55	0.94 (2, 48)	0.40	52	0.39 (2, 42)	0.68	57	1.64 (2, 50)	0.20	56	1.30 (2, 56)	0.28	89	0.72 (2, 79)	0.49	131	0.34 (2, 119)	0.71
Platinum	Dose (mg/m^2)	39	0.59 (1, 30)	0.45	27	0.69 (1, 20)	0.42	26	1.22 (1, 19)	0.28	28	3.60 (1, 22)	0.07	28	0.62 (1, 27)	0.44	42	0.47 (1, 36)	0.50	49	0.20 (1, 46)	0.66
	Agent (*Cisplatin, carboplatin*)	36	2.25 (1, 36)	0.14	25	1.29 (1, 19)	0.27	24	0.02 (1, 18)	0.88	26	0.00 (1, 23)	0.97	26	0.73 (1, 25)	0.40	37	1.77 (1, 39)	0.19	44	0.11 (1, 52)	0.74
Taxane	Dose (mg/m^2)	90	0.23 (1, 72)	0.64	45	0.29 (1, 40)	0.59	42	0.40 (1, 32)	0.53	46	0.01 (1, 44)	0.94	45	3.15 (1, 51)	0.08	77	4.67 (1, 76)	0.03	118	2.53 (1, 109)	0.11
	Agent (*Paclitaxel, docetaxel*)	87	1.74 (1, 68)	0.19	41	0.68 (1, 35)	0.41	38	2.82 (1, 29)	0.10	42	8.83 (1, 37)	**0.005**	41	6.42 (1, 41)	**0.015**	73	4.06 (1, 59)	0.05	114	1.98 (1, 102)	0.16

To access the non-adjusted outcomes for Early Cognitive Development, Intelligence, and Attention, please refer to Table S3 (Supplement). Significant results are bolded ($\alpha < 0.025$). Abbreviations: N, sample size; F, F-statistic from an F-test in the context of Type III Analysis of Variance; df, degrees of freedom; p, p-value from Type III Analysis of Variance. [a]Best-fit models included covariates maternal & paternal education level, gestational age at birth, time. [b]Best-fit models included covariates maternal & paternal educational level, time. [c]Best-fit models included covariates death mother, time. [d]Best-fit models included covariate time only. [e]Two models per group for each neurocognitive outcome, with Dose and Agent, corrected for multiple testing using Bonferroni's correction. Best-fit models were selected based on Bayesian Information Criterion (BIC).

Table 3: **Results of type III analysis of variance with Satterthwaite's method applied to linear mixed-effects regression models.[e]**

child was prenatally exposed to chemotherapy in the first trimester, which increases risk for congenital malformations.[43] These results convey reassuring child outcomes after prenatal exposure to platinum- and/or taxane chemotherapy.

An interesting finding is the association between memory and taxane type. Prenatal paclitaxel exposure was associated with lower scores on visuospatial and verbal memory, compared to docetaxel. While both taxane types are associated with neurotoxicity,[44] a possible explanation is the difference in their clearance rates. Docetaxel is metabolised to a greater extent by the enzyme CYP3A4, which is highly upregulated during pregnancy.[15,45] Consequently, lower concentrations of docetaxel may reach the foetus. Furthermore, mice dosed with paclitaxel developed distinct visuospatial learning and memory deficits.[46] When assessing the brain distribution of paclitaxel in mice, the highest levels were detected in the hippocampus, a critical region for memory.[46] This suggests that the hippocampus may be especially vulnerable to neurotoxic effects caused by paclitaxel.[44] Further studies are necessary to better understand the mechanisms underlying the differences in memory outcome related to taxane type, and to confirm this finding in larger samples. Nevertheless, it is important to acknowledge that the average outcomes for both taxane groups were within normal ranges, reducing the clinical significance of this result.

Furthermore, children whose mother had died due to cancer scored lower on attentional functioning, and children born preterm scored lower on early cognitive development. This highlights a possible indirect impact of cancer during pregnancy, and is consistent with other studies showing that early life adversity and prematurity can impact brain development.[47,48] In our cohort, 58% of children were born preterm, which is in line with the general occurrence of prematurity after cancer during pregnancy (56–61%)[25–27] and, as expected, higher than the occurrence of prematurity in the global population (10%)[49] though platinum-exposed children were born on average earlier than taxane-exposed children.

Ototoxicity is an important concern for children prenatally exposed to chemotherapy, and in particular platinum compounds.[18] In our cohort, just under 6% reported hearing loss or auditory processing impairment. While this sub-sample was too small to correlate with platinum/taxane factors, no obvious association was seen with a specific agent type. Interestingly, out of six children prenatally exposed to cisplatin and paclitaxel, four reportedly had hearing loss. All of these children were also exposed to higher doses of cisplatin (>240 mg/m^2). The auditory functioning of the platinum-exposed cohort has been documented in a distinct report (Huis in 't Veld et al., submitted). While further investigation is warranted to elucidate potential correlations between prenatal exposure to specific chemotherapy agents and ototoxicity, the findings

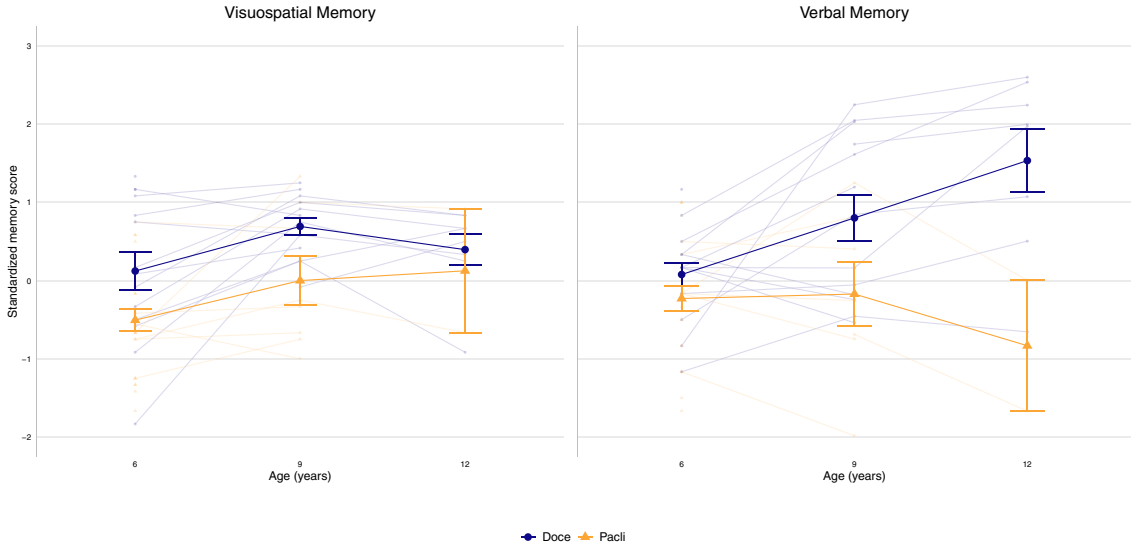

Fig. 2: Individual trajectories of standardised memory (visuospatial and verbal) score by taxane agent type, with bold lines signifying group averages. Sample size per age, per memory type, and per group (docetaxel, paclitaxel; respectively): 6 years (visuospatial: 15, 25; verbal: 15, 24), 9 years (visuospatial: 13, 8; verbal: 13, 7), 12 years (visuospatial: 8, 2; verbal: 8, 2).

underscore the importance of longitudinal audiological monitoring and early intervention in case of auditory concerns in this vulnerable population.

In our cohort, 23% needed extra neurocognitive support during their childhood. This is comparable to the general cohort of children exposed to cancer during pregnancy, where just under one-fourth required extra support at the age of 9 years,[25] and may be explained by an increased attention on the development of these children and easier access to support. Nevertheless, the prevalence of neurodevelopmental and behavioural conditions appears to be rising in the general population, with recent studies estimating that 15–20% of children aged 3–17 are affected.[50–52] The need for support was significantly associated with gestational age at birth, aligning with existing literature that shows an increased risk for neurocognitive delays and academic difficulties in preterm-born children.[53]

It is important to acknowledge the limitations of our study. Firstly, while our overall sample size was relatively large, certain subgroups were underrepresented, such as those exposed to oxaliplatin, cisplatin, or single-agent carboplatin. Further research is therefore necessary to determine whether the effect of prenatal platinum exposure is obscured by the limited sample size. Similarly, older children (>6 years) were underrepresented, which means limited conclusions can be drawn about (changes in) outcomes or diagnoses in adolescence and early adulthood.

Another potential limitation is selection bias. We were able to include 90% of all eligible children born to mothers treated with platinum- and/or taxane-based chemotherapy during pregnancy from the INCIP registry, with only 4% excluded due to foetal or neonatal death. Nevertheless, INCIP registration is voluntary and centres with greater expertise in treating cancer during pregnancy may be more inclined to register their cases and promote child follow-up, which could potentially lead to improved child outcomes. Similarly, the increased focus on the development of these children by participating centres may foster positive outcomes and facilitate early identification and intervention for developmental issues. While acknowledging that socioeconomic status may influence research participation, our cohort shows a balanced distribution of parental education levels, which helps mitigate concerns about selection bias when comparing our study group to normative populations.

Data variability is another potential issue, as some participants underwent more frequent testing based on their current age, and test versions changed over time, leading to unavoidable variations in data collection. It is important to note that the reduced number of children followed up at later ages is largely due to the interim nature of this analyses, rather than a high rate of permanent attrition, which was low (<3%), indicating that the majority of children remain engaged in the study as they age.

In conclusion, we present an interim analysis of the physical, neurocognitive, and psychosocial outcomes of the largest series of children prenatally exposed to platinum- and/or taxane-based chemotherapy, who were prospectively followed up throughout childhood in a standardised manner. Our preliminary findings are generally reassuring, with neurocognitive and

psychosocial outcomes falling within normal ranges on average across the cohort, and no observed increase in congenital malformations or chronic medical conditions. These early results suggest that platinum and taxane agents may be considered for maternal cancer treatment during pregnancy in the second and third trimesters. However, caution is warranted regarding the potential effect of paclitaxel on visuospatial and verbal memory, as well as hearing loss in this population, which necessitates further research. Additionally, given the limitations of our study, including its interim nature, further investigation is required to validate these findings in a larger sample and over a longer follow-up period.

Contributors

IAVA: data curation, formal analysis, investigation, methodology, visualisation, writing–original draft, writing–review & editing, accessed and verified underlying data.

KVC: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing–original draft, writing–review & editing, accessed and verified underlying data.

EAHiV: investigation, writing–review & editing.

MvG: investigation, writing–review & editing.

LH: investigation, writing–original draft.

CL: data curation, investigation, writing–review & editing.

EC: investigation, resources, writing–review & editing.

MJH: investigation, resources, writing–review & editing.

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FA: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing–original draft, writing–review & editing, accessed and verified underlying data.

All authors read and approved the final version of this manuscript.

Data sharing statement

Individual participant data collected during the trial, after deidentification, will be available, upon request, as well as the study protocol, statistical analysis plan, and informed consent form. This data will be available immediately following publication, for as long as the INCIP study is active, with the expected end date of 2032. Data will only be shared with INCIP members who have a methodologically sound proposal, which will be discussed within the INCIP team. Data will thus be used to achieve aims in the approved proposal. Proposals should be directed to frederic.amant@uzleuven.be. To gain access, data requestors will need to apply for INCIP membership and will need to sign a data access agreement.

Declaration of interests

CLL: Personal fellowship fundamental research contract with FWO (no. 1127523N).

FA: Personal Senior Clinical Researcher grant with FWO. Participation in the MiMARK advisory board for early detection of endometrial cancer. Chair of the International Network on Cancer, Infertility, and Pregnancy (INCIP) of the European Society of Gynecologic Oncology (ESGO), and of the Advisory Board on Cancer, Infertility and Pregnancy (ABCIP).

The remaining authors declare no conflict.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102922.

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