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This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1828422 since 2022-04-27T17:34:02Z

Published version:

DOI:10.1139/cjpp-2021-0622

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09 November 2026

GENDER-SPECIFIC SIDE EFFECTS OF CHEMOTHERAPY IN PANCREATIC CANCER PATIENTS

Running title: Gender and chemotherapy in pancreatic cancer

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ABSTRACT

Pancreatic carcinoma incidence showed a significant increase in men over the last few years and the prognosis remains poor. Patients are treated with different pharmacological plans with no evidence about gender-specific adverse effects. We aimed to investigate differences in the incidence of chemotherapy side effects in the treatment of pancreatic cancer, in order to provide insights toward a personalized assistance based in individual needs. The sample population is composed of 207 patients. Regression model highlighted the predictive role of female gender for alopecia, constipation, hand-foot syndrome and epigastric pain. Also considering single therapeutic schemes, gender differences have been reported. Moreover, evaluating the effect of age, a general reduced risk of toxicity has been reported in younger patients. In order to personalize chemotherapy and increase patients survival rate and life quality during the therapy, gender medicine and pharmacology studies are recommended.

Keywords: Gender Differences - Adverse effects - Drugs toxicity - Chemotherapy - Pancreatic carcinoma

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1. Introduction

Recent studies demonstrate gender-specific incidence, progression and severity of different tumors. Differences worth to be investigated in parameters such as body weight, fat distribution, hormonal profile, metabolism, immune response and genetics (Ghosh and Klein, 2017, Takahashi and Iwasaki, 2021). Among other physiological factors, different metabolic enzymes and specific liver and kidney transporters, concur to modulate pharmacokinetics and pharmacodynamics according to gender. Women have a slower gastric emptying time, and a bigger distribution volume for lipophilic drugs. Chemotherapy shows a 1.7 increase in adverse effects in women, although the longer half-life provide a benefit in terms of survival rate (Buoncervello et al., 2017, Anderson, 2008, Gandhi et al., 2004, Nicolson et al., 2010, Franconi et al., 2007). Analogously, women are more sensitive to toxicity, especially at gastrointestinal and mucosal level, when treated with 5-fluorouracile. Moreover, nausea and vomit are increased because of the lower efficacy of antiemetic drugs (Gabriele et al., 2016, Schmetzer and Flörcken, 2012).

In 2015 dead for pancreatic carcinoma (PC) have been 11,463, representing the fourth cause of death for women (8%) and the sixth for men (6%) (Carioli et al., 2021). There are no screenings available to date to detect potential presence of PC and it is frequently discovered by accident while doing other tests, often too late for a good prognosis. PC incidence and mortality are increasing with age in both sexes (Ilic and Ilic, 2016). It is especially a disease of the elderly, and 90% of the cases are diagnosed after 55 years of age (Malvezzi et al., 2016, Bosetti et al., 2012).

When the diagnosis of PC is confirmed by imaging techniques, the clinical approach can follow three different strategies: surgical removal of the tumor (15-20% of cases); if *"bord*erline *resectable*", surgical removal is performed after chemotherapy. Another possible strategy is the radiation therapy, frequently used in neoadjuvant, adjuvant and palliative settings (Venkatesulu et al., 2018).

In the pharmacological treatment of PC, the main chemotherapeutics are (Springfeld et al., 2019):

- Gemcitabine is the front-line chemotherapy medication, inhibits DNA synthesis. Among the most diffused collateral effects are nausea, vomit, increased transaminases, cutaneous eruption, leucopoenia, anemia, thrombocytopenia, dyspnea, alopecia, asthenia, proteinuria and

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hematuria. It is usually administered in association with abraxane (protein-bound paclitaxel) and albumin.

- Another approach is the so called FOLFIRINOX, consisting in folinic acid, 5-fluorouracile, irinotecan e oxaliplatin. Folinic acid reduces toxicity, 5-fluorouracile is an anti-metabolite with an anti-proliferative effect on cells; irinotecan is a pro-drug with an antineoplastic action and oxaliplatin is alchilating agent. Although this combination has beneficial effects, its toxicity induces mucositis, diarrhea, myelosuppression, nausea, vomit, alopecia, paresthesia e palmar-plantar erythrodysesthesia.
- Alternatives are combination of folinic acid, 5-fluorouracile and oxaliplatin (named FOLFOX) or association of folinic acid, 5-fluorouracile and irinotecan (FOLFIRI).
- Capecitabine, is a chemotherapy drug belonging to the class of antimetabolite, with side effects as anorexia, nausea, vomit, hand-foot syndrome, diarrhea, asthenia and abdominal pain.
- Cisplatin, often used in association with other drugs, blocks DNA synthesis; among adverse reaction, most common are myelosuppression, hyponatremia, renal dysfunction, nausea, vomit and alopecia.
- Cetuximab is a new drug of the promising category of monoclonal antibodies; they act on specific receptors with minimal side effects. Although reduced, major reactions consist of cutaneous rushes diarrhea, nausea and vomit.

Side effects vary, are patient-specific and not necessarily evident thus more attention must be paid to age and gender-specific differences. According to the 2016 recommendations of the Italian Ministry of Health and to the most recent "*Plan for the application and diffusion of gender medicine*", specific vigilance must be provided in order to monitor gender-specific side effects of chemotherapeutical drugs. As for today, no scientific communication reports data about the incidence of gender-specific side effects of chemotherapeutic drugs for PC although significant differences are filed during at diagnosis with 51,1% of diagnosed women versus 48,9% men and the above mentioned gap in mortality (Carioli et al., 2021). Moreover, a lack of study in elderly lead to a difficult management in patients with particular drugs pharmacodynamics and pharmacokinetic changes (Higuera et al., 2016).

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90 The aim is to identify age and gender-specific toxicity of chemotherapeutic drugs in patients affected
91 by PC in order to provide insights toward a personalized assistance based on individual needs.

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2. Materials and methods

We performed a retrospective observational study in PC diagnosed patients, enrolled at the Medical Oncology Day Hospital of the Molinette Hospital Unit, AOU City of Health and Science of Turin, from October 2017 to June 2019. Inclusion criteria were PC diagnosis, active therapy, age ≥ 18 years old and Day Hospital exclusive affiliation. Data have been matched to two different ranking systems: TNM for tumor staging and *Common Terminology Criteria for Adverse Events* (CTCAE) for toxicity (nausea, vomit, neurotoxicity, alopecia, asthenia, diarrhea, constipation, "hand-foot" syndrome, epigastralgy, dysgeusia, thrombocytopenia, epistasis, mucositis and neutropenia) (Basch et al., 2014).

2.1 Statistical analysis

Continuous variables were described using mean and standard deviations (SD) or median and interquartile range (IQR) according to their distribution. Categorical variables were described using frequencies and percentages. Differences between males and females were tested performing the Mann-Whitney U test or the Fisher exact test, when appropriate. Multivariate logistic regression models, adjusted by age, were computed to evaluate the association between sex and risk of toxicity during chemotherapy treatment. The Huber-White estimator was used to adjust for the correlation between the multiple observations on the same patient. Odds Ratios (OR) and 95% confidence intervals (95% CI) were reported. Firth's correction was applied to reduce the bias of the estimates due to small number of events. Statistical analyses were performed using *IBM SPSS Statistics 22.0* per Windows (Chicago, Illinois, USA). The level of significance was set at 0.05.

2.2 Ethical considerations

These data were routinely recorded during daily clinical practice as a quality assurance measure and to explore improvements in the quality of services; therefore, ethics committee approval was not required. Confidentiality was guaranteed in data collection, analysis and dissemination phase, presenting the results in aggregate form.

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3. Results

3.1 Study Population

Sample population consists of 207 patients, for a total hospital accesses of 3489 days. Table 1 reports baseline characteristics of the enrolled patients. Statistically significant differences have been observed between the two genders on median age: 65.74 years (IQR 62-71.75 years) considering females and 60.55 years (IQR 51-65 years) for males ($p < 0.001$).

3.2 Association of age and sex with toxicity

Describing toxicities collected every access and considering all the therapeutic regimens, statistically significant differences have been observed in the prevalence of alopecia (25% females and 9.5% males, $p < 0.001$), constipation (64.3% females and 40.5% males, $p = 0.006$), hand-foot syndrome (28.6% females and 11.9% males, $p = 0.004$) and epigastralgy (39.3% and 23.8%, $p = 0.006$). The distribution of toxicity episodes per patients and adverse events grade, stratified by sex, is shown in table 2. Figure 1 describes the main adverse events distribution, stratified by sex. Figure 2 shows the distribution of toxicity in females and males, respectively.

Using a multivariate regression model, we described the gender-related risk of adverse events. Females have an increased risk of alopecia (OR (95%CI): 0.216 (0.087 – 0.540), $p = 0.001$), constipation (OR (95%CI): 0.292 (0.155 – 0.550), $p < 0.001$), hand-foot syndrome (OR (95%CI): 0.259 (0.113 – 0.595), $p = 0.001$) and epigastralgy (OR (95%CI): 0.337 (0.172 – 0.660), $p = 0.002$). Moreover, younger patients have a reduced risk for fever (OR (95%CI): 1.054 (1.013 - 1.097), $p = 0.009$).

3.3 Association of age and sex with gemcitabine-related toxicities

Forty-six patients undergone gemcitabine treatment (Figure 3A), for a mean number of cycles of 6.32 (median 5, IQR 1-1.75), 26 (56.5%) females and 20 (43.5%) males. Statistically significant differences have been observed in the prevalence of nausea (7.7% females and 40% males $p = 0.008$), vomit (0% females and 20% males, $p = 0.018$) and epigastralgy (42.3% and 10%, $p = 0.017$) (Figure 2A). Instead, considering the toxicity risk, females resulted at a significant increased risk of nausea (OR (95%CI): 7.794 (1.420 - 42.779), $p = 0.018$) and epigastralgy (OR (95%CI): 0.121 (0.021 -

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0.710), p = 0.019) and younger patients had a minor risk to feel pain (OR (95%CI): 0.917 (0.849 - 0.990), p = 0.027).

3.4 Association of age and sex with folfiri plan-related toxicities

Twenty-nine patients undergone folfiri chemotherapy scheme (Figure 3B), for a mean number of cycles of 5.27 (median 5, IQR 1.75-5.25), 16 (55.2%) females and 13 (44.8%) males. Statistically significant differences have been observed in the prevalence of alopecia (31.3% females and 0% males p = 0.030) and hand-foot syndrome (37.5% females and 0% males, p = 0.016) (Figure 2B).

3.5 Association of age and sex with FOLFOX plan-related toxicities

Only eleven patients undergone folfox plan (Figure 3C), for a mean number of cycles of 5.27 (median 6, IQR 3-7), 6 (54.5%) females and 5 (45.5%) males. Constipation prevalence is higher in females (83.3%), than in males (0%) (p = 0.032) (Figure 2C).

3.6 Association of age and sex with oxapetrelli plan-related toxicities

In a total of 31 patients undergoing oxapetrelli therapeutic scheme, for a mean number of cycles of 4.89 (median 4, IQR 3-6), 21 (67.7%) females and 10 (23.3%) males, significant differences have been observed between the two genders on median age: 68 years (IQR 63-73 years) considering females and 57 years (IQR 51-64.25 years) for males (p = 0.006). Younger patients resulted at a significant increase risk of vomit (OR (95%CI): 1.173 (1.006 - 1.366), p = 0.041) and constipation (OR (95%CI): 1.025 (0.928 - 1.132), p = 0.024).

3.7 Association of age and sex with gemcitabine-abraxane plan-related toxicities

Forty-seven patients undergone gemcitabine and abraxane treatment scheme (Figure 3D), for a mean number of cycles of 4.39 (median 2, IQR 1-6), 26 (53.3%) females and 21 (44.7%) males. Gender related prevalence of alopecia (42.3% females and 14.3% males p = 0.034) and icterus (0% females and 19% males, p = 0.021) (Figure 2D). Considering the toxicity risk, younger subjects have reduced risk of fever (OR (95%CI): 1.148 (1.044 - 1.263), p = 0.005).

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4. Discussion

Aside from gender-specific tumors (breast, prostate, ovarian cancer), recent studies demonstrate gender-specific incidence, progression and severity of different tumors. Differences have to be investigated in parameter such as body weight, fat distribution, hormonal profile, metabolism, immune response and genetics (Ghosh and Klein, 2017, Takahashi and Iwasaki, 2021). Among other physiological factors, different metabolic enzymes and specific liver and kidney transporters, concur to modulate pharmacokinetics and pharmacodynamics according to gender. Women have a slower gastric emptying time, and a bigger distribution volume for lipophilic drugs. Chemotherapeutical compounds show, thus, a 1.7 increase in adverse effects in women, although the longer half-life provide a benefit in terms of survival rate (Buoncervello et al., 2017, Anderson, 2008, Gandhi et al., 2004, Nicolson et al., 2010, Franconi et al., 2007, Wagner et al., 2019). Analogously, women are more sensitive to toxicity, especially at gastrointestinal and mucosal level, when treated with 5-fluorouracile. Moreover, nausea and vomit are increased because of the lower efficacy of antiemetic drugs (Gabriele et al., 2016, Schmetzer and Flörcken, 2012). A gender analysis, therefore, is a necessary condition to arrive at the equity of care: crucial necessity in clinical settings such as oncology, where extensive and very toxic drugs are widely used. Sex-specific analyses are of primary importance to establish targeted anti-cancer drug regimen (Azap et al., 2021, Nipp et al., 2018). We analyzed 98 PC patients in order to identify gender-specific toxicity of chemotherapeutic drugs administered to treat PC. In general, the female gender seems to be predominantly affected by all the toxicities considered, especially for alopecia, constipation, hand-foot syndromes and epigastralgy. In addition, nausea, vomit and icterus were observed more frequently in men. In addition, PC has a higher incidence in the elderly: at diagnosis the median age is 70 years old, 65 in our cohort, were the is not a specific sample selection regarding age. In elderly patients, changes in functions and physiology of the entire organism could interfere with the drugs pharmacokinetic, leading to drug over/underexposure, treatment failure or toxicity events. Moreover, they present more comorbidities, organ impairment and a general reduced life expectancy. Although chemotherapy improves PC patients survival, these patients are underrepresented in clinical trials and a few information have been collected about treatment outcome and chemotherapy related adverse events in patients over 65 years of age (Yip et al., 2006, Hutchins et al., 1999). Different studies

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reported the increased efficacy of gemcitabine-base regimens, but with a dramatic increase of adverse events (Jin et al., 2018, Kuroda et al., 2017, Imaoka et al., 2016). Similar results have been observed for FOLFIRINOX and for the combination of abraxane and gemcitabine: neutropenia, fatigue, vomiting, and diarrhoea frequencies increased from 5.3% to 42.5% (Von Hoff et al., 2013, Conroy et al., 2013). Recently, Kim and colleagues, in a study on 97 PC patients undergoing FOLFIRINOX regimen, observed that median overall survival was longer in females, suggesting a better outcome in this patients. Moreover, they reported a significant difference in the age-corrected dose reduction pattern: females receive 90% of the initial dose in the first cycle and the 65% in 1 year, males the 95% and 83%n respectively. However, they did not observed gender differences regarding chemotherapy-related toxicities (Kim et al., 2021).

Concluding, chronological age is an important variable in chemotherapy end for cancer patients management. For this reason, further studies in elderly are necessary to reduce suboptimal treatment.

This study has limitations. First, it was a retrospective and single centre study. No data about comorbidities, drug dose or scheme modification have been reported. Comorbidities information is necessary to confirm the evidence reported in this study. Moreover, information about androgenic alopecia incidence before the start of the chemotherapy in our population is lacking; this can interfere with the obtained results, thus further studies including data about alopecia and its genetic predisposition are warranted (Rinaldi et al., 2019).

Medicine without any categorization by sex, gender and age is methodologically incorrect. An age and gender-based approach to clinical practice seems to be mandatory, as it could significantly contribute to health promotion by improving the effectiveness of diagnostic and/or therapeutic approaches and, therefore, leading to important benefits primarily for the patients but also for the sustainability of the National Health System.

5. Conclusions

Given the biological and socio-cultural differences between genders, gender-specific analyses should be conducted to provide optimal cancer prevention strategies, to reduce the number of new PC cases and to better provide treatment both in men and women. Vision that would change oncology setting of PC, a stable disease but still orphan of a real tailored approach

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223 **Competing interest:** The authors declare there are no competing interest.
224
225 **Contributors' statement:** Conceptualization: SDF; PB; TA; SS; SR; MVM. Data curation: PB; SA;
226 GS; FC; JC. Formal analysis and methodology: PB; SA. Writing - original draft: SDF; DM; SA.
227 Supervision: SDF; LC; MVM. Writing – review & editing: TA; SS; SR; LC; MVM.
228
229 **Funding:** The authors declare no specific funding for this work.
230
231 **Data Availability Statement:** Data sharing not applicable to this article as no datasets were generated
232 or analysed during the current study.

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FIGURE LEGENDS

Figure 1. Distribution of main chemotherapy adverse effect. Black: female patients; gray: male patients.

Figure 2. **Panel A** Distribution of main chemotherapy adverse effect in female patients (N=138). **Panel B** Distribution of main chemotherapy adverse effect in male patients (N=88).

Figure 2. **Panel A** Distribution of gemcitabine-related toxicities (N=46). Black: female patients (n=26); gray: male patients (N=20). **Panel B** Distribution of folfiri-related toxicities (N=29). Black: female patients (n=16); gray: male patients (N=13). **Panel C** Distribution of folfox-related toxicities (N=11). Black: female patients (n=6); gray: male patients (N=5). **Panel D** Distribution of gemcitabine-abraxane plan-related toxicities (N=47). Black: female patients (n=26); gray: male patients (N=21).

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Table 1. Baseline characteristics of the enrolled patients

Baseline characteristic	
Hospital accesses	3489
Enrolled p*atients* n, *%*	207, 100
Mean *Age, median (IQR)*	63.56, 65 (56-70)
Female patients n, *%*	120, 58
M*ale patients* n, *%*	87, 42

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Table 2. Distribution of toxicity episodes stratified by sex

Adverse effect	Total (%)	F (%)	M (%)	*P-value*
Nausea				
Absent	72 (73.4%)	44 (78.6%)	28 (66.7%)	0.099
Present	26 (26.6%)	12 (21.4%)	14 (33.3%)	
Grade 1 N (%)	17 (17.4%)	9 (16%)	8 (19%)	
Grade 2 N (%)	9 (9.2%)	3 (5.4%)	6 (14.3%)	
Grade 3 N (%)	0	0	0	
Grade 4 N (%)	0	0	0	
Vomit	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	86 (87.7%)	51 (91%)	35 (83.3%)	0.172
Present	12 (12.3%)	5 (9%)	7 (16.7%)	
Grade 1 N (%)	9 (9.2%)	4 (7.2%)	5 (11.9%)	
Grade 2 N (%)	3 (3.1%)	1 (1.8%)	2 (4.8%)	
Grade 3 N (%)	0	0	0	
Grade 4 N (%)	0	0	0	
Neurotoxicity	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	60 (61.2%)	34 (60.7%)	26 (62%)	0.524
Present	38 (38.8%)	22 (39.3%)	16 (38%)	
Grade 1 N (%)	23 (23.5%)	12 (21.4%)	11 (26.2%)	
Grade 2 N (%)	14 (14.3%)	9 (16.1%)	5 (11.8%)	
Grade 3 N (%)	1 (1%)	1 (1.8%)	0	
Grade 4 N (%)	0	0	0	
Pain	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	46 (46.9%)	25 (44.6%)	21 (50%)	0.715
Present	52 (53.1%)	31 (55.4%)	21 (50%)	
Icterus	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	88 (89.8%)	51 (91.2%)	37 (88.1%)	0.833
Present	10 (10.2%)	5 (8.8%)	5 (11.9%)	
Alopecia	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	80 (81.6%)	42 (75%)	38 (90.5%)	**0.001**
Present	18 (18.4%)	14 (25%)	4 (9.5%)	
Grade 1 N (%)	10 (10.2%)	8 (14.3%)	2 (4.7%)	

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Grade 2 N (%)	6 (6.1%)	4 (7.1%)	2 (4.8%)	
Grade 3 N (%)	2 (2.1%)	2 (3.6%)	0	
Grade 4 N (%)	0	0	0	
Asthenia	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	51 (52%)	29 (51.8%)	22 (52.4%)	
Present	47 (48%)	27 (48.2%)	20 (47.6%)	
Grade 1 N (%)	17 (17.3%)	7 (12.5%)	10 (23.8%)	0.565
Grade 2 N (%)	28 (28.6%)	19 (33.9%)	9 (21.4%)	
Grade 3 N (%)	2 (2.1%)	1 (1.8%)	1 (2.4%)	
Grade 4 N (%)	0	0	0	
Diarrhea	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	71 (72%)	38 (67.9%)	33 (78.6%)	
Present	27 (28%)	18 (32.1%)	9 (21.4%)	
Grade 1 N (%)	11 (11.2%)	7 (12.5%)	4 (9.5%)	0.054
Grade 2 N (%)	14 (14.3%)	10 (17.9%)	4 (9.5%)	
Grade 3 N (%)	2 (2,5%)	1 (1.7%)	1 (2.4%)	
Grade 4 N (%)	0	0	0	
Constipation	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	45 (45.9%)	20 (35.7%)	25 (59.5%)	
Present	53 (54.1%)	36 (64.3%)	17 (40.5%)	
Grade 1 N (%)	22 (22.4%)	17 (30.4%)	5 (11.9%)	**0.006**
Grade 2 N (%)	30 (30.6%)	19 (33.9%)	11 (26.2%)	
Grade 3 N (%)	1 (1.1%)	0	1 (2.4%)	
Grade 4 N (%)	0	0	0	
Hand-foot syndrome	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	77 (78.6%)	40 (71.4%)	37 (88.1%)	
Present	21 (21.4%)	16 (28.6%)	5 (11.9%)	
Grade 1 N (%)	10 (10.2%)	7 (12.5%)	3 (7.1%)	**0.004**
Grade 2 N (%)	10 (10.2%)	8 (14.3%)	2 (4.8%)	
Grade 3 N (%)	1 (1%)	1 (1.8%)	0	
Grade 4 N (%)	0	0	0	
Epigastralgy	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	66 (67.3%)	34 (60.7%)	32 (76.2%)	
Present	32 (32.7%)	22 (39.3%)	10 (23.8%)	**0.006**
Grade 1 N (%)	28 (28.6 %)	20 (35.7%)	8 (19%)	

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Grade 2 N (%)	3 (3.1%)	2 (3.6%)	1 (2.4%)	
Grade 3 N (%)	1 (1%)	0	1 (2.4%)	
Grade 4 N (%)	0	0	0	
Dysgeusia	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	92 (93.9%)	52 (92.9%)	40 (95.2%)	
Present	6 (6.1%)	4 (7.1%)	2 (4.8%)	
Grade 1 N (%)	3 (3.1%)	2 (3.5%)	1 (2.4%)	0.523
Grade 2 N (%)	2 (2%)	1 (1.8%)	1 (2.4%)	
Grade 3 N (%)	1 (1%)	1 (1.8%)	0	
Grade 4 N (%)	0	0	0	
Thrombocytopenia	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	81 (82.6%)	45 (80.4%)	36 (85.7%)	
Present	17 (17.4%)	11 (19.6%)	6 (14.3%)	
Grade 1 N (%)	5 (5.1%)	3 (5.4%)	2 (4.8%)	0.213
Grade 2 N (%)	8 (8.2%)	5 (8.8%)	3 (7.1%)	
Grade 3 N (%)	4 (4.1%)	3 (5.4%)	1 (2.4%)	
Grade 4 N (%)	0	0	0	
Epistasis	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	89 (90.8%)	51 (91.1%)	38 (90.5%)	
Present	9 (9.2%)	5 (8.9%)	4 (9.5%)	
Grade 1 N (%)	3 (3.1%)	2 (3.6%)	1 (2.4%)	0.481
Grade 2 N (%)	4 (4.1%)	2 (3.5%)	2 (4.7%)	
Grade 3 N (%)	2 (2%)	1 (1.8%)	1 (2.4%)	
Grade 4 N (%)	0		0	
Mucositis	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	91 (92.9%)	51 (91.1%)	40 (95.2%)	
Present	7 (7.1%)	5 (8.9%)	2 (4.8%)	
Grade 1 N (%)	5 (5.1%)	4 (7.1%)	1 (2.4%)	0.312
Grade 2 N (%)	2 (2%)	1 (1.8%)	1 (2.4%)	
Grade 3 N (%)	0	0	0	
Grade 4 N (%)	0	0	0	
Fever	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	78 (79.6%)	44 (78.6%)	34 (80.9%)	0.473
Present	20 (20.4%)	12 (21.4%)	8 (19.1%)	
Neutropenia	**Total (%)**	**F (%)**	**M (%)**	***P-value***

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Absent	69 (70.4%)	40 (71.4%)	29 (69%)	0.999
Present	29 (29.6%)	16 (28.6%)	13 (31%)	
Grade 1 N (%)	6 (6.1%)	4 (7.1%)	2 (4.8%)	
Grade 2 N (%)	7 (7.1%)	3 (5.4%)	4 (9.6%)	
Grade 3 N (%)	13 (13.3%)	7 (12.5%)	6 (14.2%)	
Grade 4 N (%)	3 (3.1%)	2 (3.6%)	1 (2.4%)	
Anemia	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	81 (82.7%)	45 (80.4%)	36 (85.8%)	0.123
Present	17 (17.3%)	11 (19.6%)	6 (14.2%)	
Weight loss	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	79 (80.6%)	45 (80.4%)	34 (80.9%)	0.631
Present	19 (19.4%)	11 (19.6%)	8 (19.1%)	
Diabetes	**Total (%)**	**F (%)**	**M (%)**	***P-value***
Absent	93 (94.9%)	54 (96.4%)	39 (92.9%)	0.239
Present	5 (5.1%)	2 (3.6%)	3 (7.1%)	

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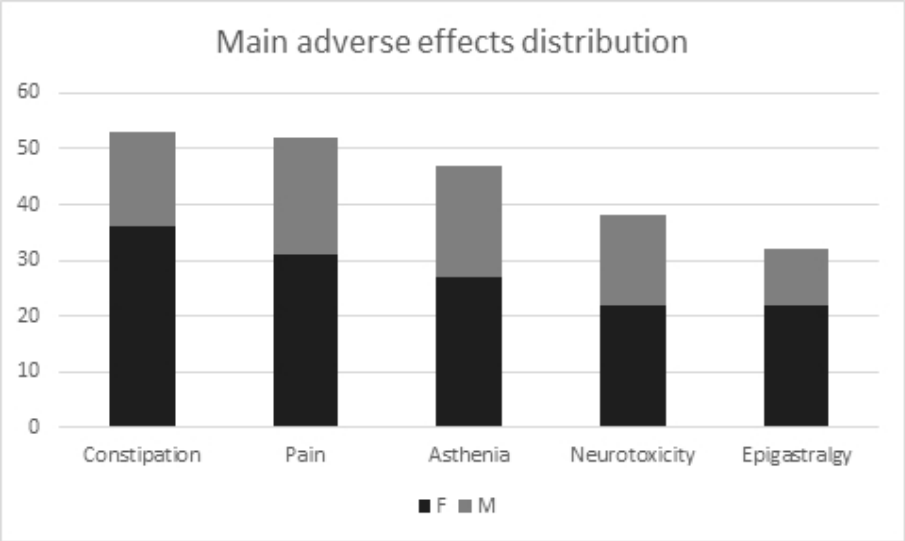

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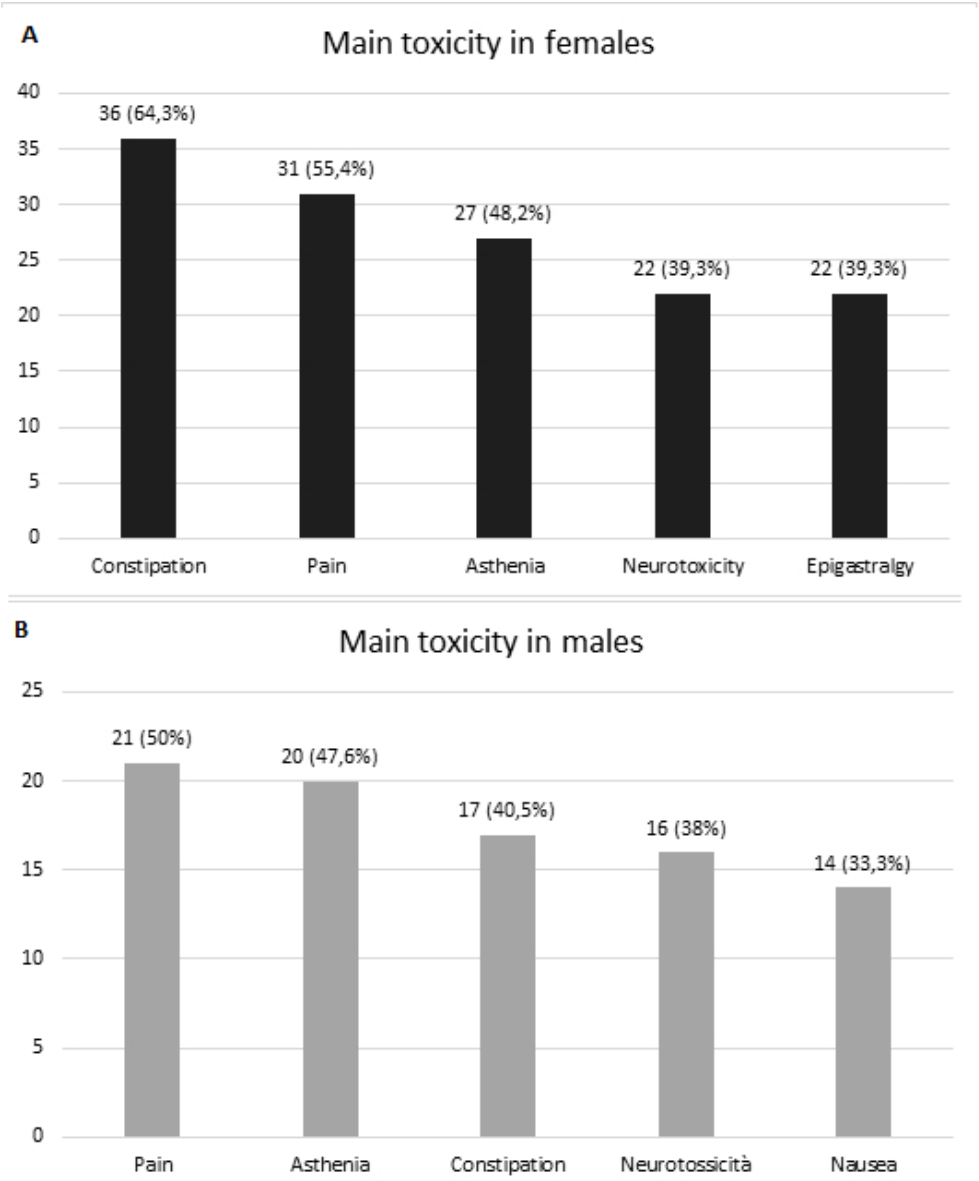

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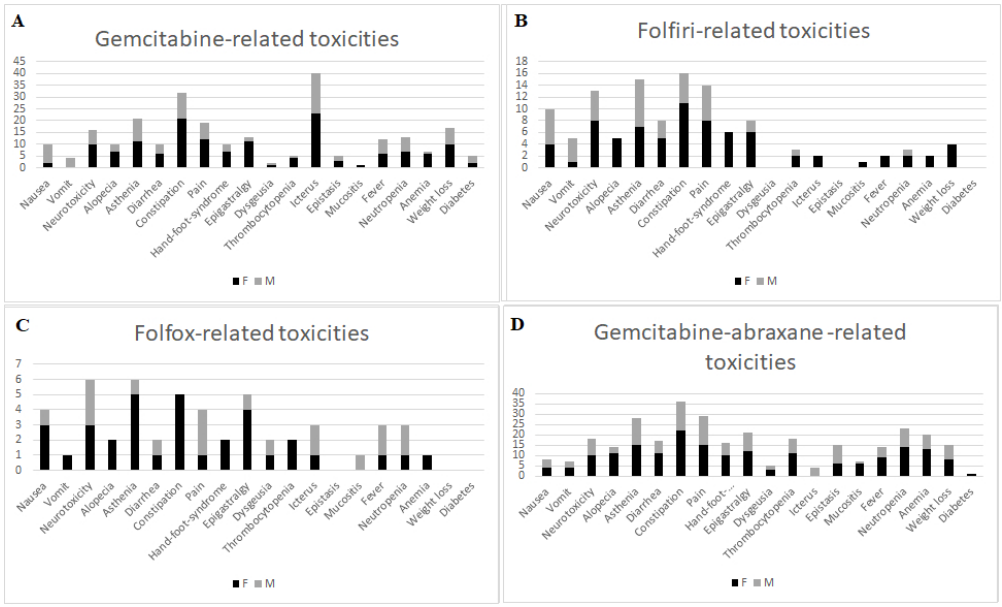

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