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Preoperatory FLOT Regimen for Gastroesophageal Cancer and Renal Function: A New Onco-Nephrological Perspective

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Keywords
FLOT · Oxaliplatin · Acute kidney disease

Abstract

Background: The FLOT regimen, a combination of fluorouracil, leucovorin, oxaliplatin, and docetaxel, is a standard treatment for gastric and esophagogastric junction cancers, but concerns exist about its potential renal toxicity. The exact prevalence and severity of renal toxicity need to be well documented, and this knowledge gap could impact the optimal use of the FLOT regimen in clinical practice. We aimed to evaluate the renal toxicity profile of the FLOT regimen with a specific focus on acute kidney disease (AKD) onset in a real-life setting and explore associated risk factors. ***Methods:*** We conducted a multicenter retrospective study involving 96 patients treated with preoperatory FLOT. The incidence of AKD and potential risk factors were identified. ***Results:*** AKD occurred in 3 patients (incidence rate of 0.0122 cases/month of follow-up). Oral antidiabetic agents and prostate hypertrophy emerged as significant predictors of AKD. ***Conclusion:*** AKD is uncommon in patients treated with the preoperatory FLOT regimen. Our findings highlight the importance of diligent renal function monitoring and appropriate preventive strategies in patients undergoing FLOT treatment. These results encourage the conduction of further studies and clinical experience in larger populations and patients with lower baseline estimated glomerular filtration rate.

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Plain Language Summary

The article explores the renal implications of the FLOT chemotherapy regimen in patients with gastroesophageal cancer. Focusing on the prevalence and risk of acute kidney disease (AKD) in patients undergoing preoperative FLOT treatment, the study encompassed 96 patients across various centers. It identified oral antidiabetic agents and prostate hypertrophy as potential risk factors for AKD. The findings indicate a relatively low incidence of AKD among these patients, highlighting the necessity of meticulous renal function monitoring and the implementation of preventive strategies. These insights can help inform clinicians in managing renal risks associated with FLOT treatment, potentially enhancing patient safety. This study marks a significant contribution to the field of onco-nephrology, shedding light on the renal safety of FLOT therapy. It encourages further investigations and broader application of the FLOT regimen in diverse patient groups, especially those with lower baseline estimated glomerular filtration rates.

Introduction

Gastric cancer (GC) and esophagogastric junction cancers (ECJ) collectively rank as the fifth most common cancer and the third leading cause of cancer-related deaths worldwide, constituting a global health problem [1]. Notably, Eastern Asia has the highest incidence rates for both sexes, with males having a higher incidence rate than females[1]. Diagnosis often occurs at the metastatic stage, warranting palliative chemotherapy to prolong survival and maintain quality of life.

Introducing targeted agents, such as human epidermal growth factor receptor-2 (HER2)-directed therapies and immune checkpoint inhibitors (ICIs), in conjunction with standard chemotherapy, has improved survival rates [2]. However, the prognosis of advanced disease remains grim, with only 10% of patients surviving beyond 2 years [2, 3]. The quest for new therapeutic targets and more effective drug combinations aims to enhance patient outcomes. In cases of stage II or III disease, surgery remains the primary curative treatment, and perioperative approaches have demonstrated significant improvements in survival rates and reduction in recurrence rates compared to surgery alone [4, 5].

Concerning current clinical practice management in a perioperative setting, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) and FNCLCC/FFCD trials were the first to explore this treatment strategy [4, 5]. Both trials randomized patients with G/EGJ adenocarcinoma to either surgery alone or perioperative chemotherapy. The treatment was based on epirubicin, cisplatin, and fluorouracil (ECF) in MAGIC and cisplatin plus fluorouracil in the FNCLCC/FFCD. Five-year survival rates were notably higher in the perioperative-chemotherapy group than in the surgery group.

Given the significant toxicities associated with these combination regimens, it was suggested to replace cisplatin with oxaliplatin. Oxaliplatin is associated with lower incidences of alopecia, thromboembolism, and renal toxicity but slightly higher incidences of grade 3 or 4 diarrhea and neuropathy [6, 7].

The FLOT regimen, a combination of fluorouracil, leucovorin, oxaliplatin, and docetaxel, was evaluated in the phase III FLOT4-AIO trial. It demonstrated superior efficacy as perioperative therapy compared to ECF in G/GEJ adenocarcinoma, with a median overall survival (OS) of 50 months vs. 35 months and a pathological complete regression (PCR) rate of 16% vs. 6% in the FLOT arm vs. ECF arm respectively [8, 9].

Based on these survival and safety data, the FLOT regimen has been established as the new gold standard and is currently used in clinical practice in the perioperative setting. However, while its neurotoxic side effects have been extensively studied [10], the potential nephrotoxicity remains underexplored. The highest nephrotoxic potential in the FLOT regimen derives from oxaliplatin, a platinum-based agent. Platinum-related kidney damage may be due to its accumulation in the kidneys, caused by a disruption in the balance between organic cation transporters (OCTs) on the proximal renal tubules' basolateral membranes and multidrug and toxin extrusion (MATE) transporters on the brush border membranes [11–13]. This leads to increased contact with these substances, triggering complex signal pathways that can result in inflammation, blood vessel, and oxygen-related damage, ultimately harming the tubules and cell death [14]. Compared to other platinum drugs, especially cisplatin, oxaliplatin is less harmful to the kidneys; although not fully understood, the potential mechanism may depend from a MATE-mediated expulsion of the drug from the tubular cells [15].

Surprisingly, most studies in the literature are limited to acute kidney injury (AKI) onset derived from platinum-based regimens, with a scarce focus on the renal effects that patients could experience in a broader extension of time [11, 16–20]. One of the most insidious nephrological clinical conditions is represented by acute kidney disease (AKD) establishment, which is defined as

Table 1. Descriptive statistics of the cohort: continuous variables

Continuous variables	Mean	Standard deviation (±)
Age, years	65.92	10.57
Height, cm	166.9	8.84
Weight, kg	68.32	13.33
BMI	24.43	4.06
Baseline eGFR, mL/min/1.73 m^2	85.69	16.69
eGFR slope, mL/min/1.73 m^2 per month	0.64	4.16
Urea, serum, mg/dL	28.6	13.5
Hemoglobin, g/dL	12.68	1.87
White blood cell count, total, *n*/mm^3	7,451.04	1,831.80
Neutrophils, *n*/mm^3	5,124.17	1,971.88
Lymphocytes, *n*/mm^3	1,884.27	925.07
Calcium, serum, mg/dL	9.22	0.39
Sodium, serum, mmol/L	140.55	1.88
Potassium, serum, mmol/L	4.31	0.48
Creatinine, serum, mg/dL	0.90	0.21

BMI, body mass index; eGFR, estimated glomerular filtration rate.

an acute or subacute impairment of renal function for a duration of between 7 and 90 days after exposure to an AKI starting event [21, 22]. Unfortunately, AKD can be relevant for the clinical management of cancer patients as AKI because prolonged renal dysfunction during the platinum regimens can compromise the efficacy of therapy due to the reduction of dose or, in the worst cases, due to the disruption of the treatment.

Our multicenter clinical study aimed to better elucidate the real-life acute nephrotoxicity of the preoperatory FLOT regimen, with a particular focus on the AKD onset, to offer clinicians clues about this regimen's renal risks, ultimately enhancing patient safety and comfort when treating GC and EGJ.

Materials and Methods

Data Sources

The study utilized a comprehensive dataset from four high-volume medical centers in Italy (IRCCS San Raffaele Scientific Institute, Milan; Policlinico di Milano, Milan; Università degli Studi di Cagliari and Ospedale Oncologico A. Businco, Cagliari). The collected data encompassed various aspects of patient demographics, details of drug prescriptions, clinical events, and lifestyle variables (see Tables 1, 2). Each patient's treatment was traced from the beginning of the therapy (FLOT regimen), through each treatment cycle (in total, 4), to the end of treatment or data collection. The preoperative FLOT regimen consists of four 2-week cycles of docetaxel 50 mg/m^2, intravenous oxaliplatin 85 mg/m^2, intravenous leucovorin 200 mg/m^2, and fluorouracil 2,600 mg/m^2 as a 24 h infusion, all on day 1 [8, 9]. The dataset included longitudinal measurements of clinical parameters and labs (e.g., hemoglobin, white blood cell count, neutrophils, lymphocytes, calcemia, sodium, potassium, creatinine, etc.) taken during each cycle of the FLOT regimen.

Patient Informed Consent and Ethical Approval

The study adhered to the guidelines outlined in the Declaration of Helsinki.

Study Population

The study population comprised a cohort of patients affected with gastric cancer who underwent the FLOT regimen between January 1, 2020, and December 31, 2023 – the inclusion criterion required all patients to be at least 18 years old when initiating the FLOT treatment. To ensure the validity and reliability of the study results, we excluded patients with a history of any other cancers (other than non-melanoma skin cancer), end-stage renal disease, active liver diseases, active systemic connective tissue diseases, and any drug abuse.

Table 2. Descriptive statistics of the cohort: categorical variables

Categorical variables	Patients (N = 96)	Percentage
Gender (male)	61	63.54
Diabetes	6	5.21
Hypertension	38	35.42
Cardiovascular diseases	9	9.38
Smoking status	26	27.08
Alcohol use	1	1.04
Liver disease	3	3.13
Prostate hypertrophy	4	4.17
Thrombophilia	5	5.21
RAAS inhibitors	12	12.5
Thyroid hormones	4	4.17
Nutritional supports	13	12.48
Beta blockers	10	10.42
Calcium antagonist	8	8.83
Diuretics	5	5.21
ASA	7	7.29
Oral antidiabetic agents	3	3.13
Insulin	1	1.04
PPI	40	41.67
NSAIDS	10	10.42

RAAS, renin angiotensin aldosterone system; ASA, acetylsalicylic acid; PPI, proton pump inhibitors; NSAIDS, nonsteroidal anti-inflammatory drugs.

Selection of Cases

For this study, we did a retrospective cohort study. The study follows these patients longitudinally, tracking their treatment and health markers from the beginning of the FLOT regimen to the end of treatment or data collection. Cases were constituted by patients who developed AKD during the FLOT regimen. The current AKD definition includes the onset of AKI or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, or eGFR decrease by ≥35%, or serum creatinine (SCr) increase by 50% occurring less than 90 days after the possible insult [21]. The functional criteria utilized for AKI, AKD, and chronic kidney disease (CKD) definitions, according to KDIGO guidelines [21], are summarized in Table 3. It is essential to underline that no patients experienced ESRD requiring hemodialysis after therapy as well as recovery in the intensive care unit to treat a severe grade of AKI.

Potential Confounders

The risk estimates were adjusted for various comorbidities (e.g., cardiovascular disease, diabetes, hypertension, etc.), drugs known to be associated with AKD (e.g., RAAS inhibitors, diuretics, etc.) that could also influence the use of the FLOT regimen, and lifestyle factors (e.g., alcohol, smoke, elevated BMI, etc.) (Table 2).

Statistical Analysis

Descriptive Statistics

Descriptive statistics were generated for all variables in the dataset. Continuous variables were summarized using measures of central tendency (mean, median) and dispersion (standard deviation, interquartile range) according to data distribution. In contrast, categorical variables were summarized using frequencies and percentages (Tables 1, 2).

Incidence Rate Calculation

The incidence rate of AKD was estimated by dividing the total number of cases by the total number of person-years of follow-up. The person-years of follow-up were calculated as the sum of follow-up time for all patients from the start of the treatment until AKD, death, or end of the follow-up period, whichever occurred first. Confidence intervals for the incidence rate were estimated based on the Poisson distribution, which is appropriate for rare events like, in our case, AKD.

Univariate Analysis

Univariate logistic regression models examined the relationship between each independent variable and the outcome of interest (AKD). This step initially understood the relationship between each covariate and the binary work.

Multivariate Analysis

A multivariate logistic regression model included all variables significantly associated with the outcome. The model produced adjusted odds ratios (ORs) that estimated the association between the exposure (FLOT regimen) and the product (AKD), controlling for all other variables in the model. The fit of the logistic regression model was checked using various diagnostics. The Hosmer-Lemeshow goodness-of-fit test was used to assess whether the observed event rates match expected event rates in subgroups of the model population. Variance Inflation Factor (VIF) was used to check for multicollinearity among the independent variables. Finally, a stepwise logistic regression was performed.

All statistical analyses were two-tailed, and a p value of <0.05 was considered statistically significant. We analyzed data using IBM SPSS Statistics software (version

Table 3. Functional criteria for kidney diseases

Definition	KDIGO-AKI	KDIGO-AKD	KDIGO-CKD
	sCr increase≥ 0.3 mg/dL within 48 h or Increase in sCr ≥1.5 × baseline that is known or presumed to have occurred within the past 7 days	AKI or eGFR decrease <60 mL/min/1.73 m^2 or eGFR decrease by ≥35% or eGFR increase by 50% occurring from less than 90 days	eGFR < 60 mL/min/ 1.73 m^2 > 3 months

AKI, acute kidney injury; SCr, serum creatinine; AKD, acute kidney disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Table 4. Incidence rate of acute kidney disease (AKD) in the study population

Total AKD cases	Total follow-up time, months	Incidence rate, cases/month	95% CI
3/96	288	0.0104	0.00–0.0243

All patients ended the regimen (3 months), leading to 288 months of total follow-up.

28, IBM Corp., Armonk, NY, USA) and the R statistical software environment (version 4.1.1, R Core Team, Vienna, Austria).

Results

Study Population and Descriptive Statistics

Our research targeted a selected cohort of 96 consecutive patients diagnosed with gastric cancer undergoing the FLOT chemotherapy regimen between January 1, 2020, and December 31, 2023, enrolled in four high-volume medical centers in Italy. The diverse patient pool enriched the depth of our study, reflecting a broad spectrum of cases from the wider population, thereby improving the generalizability of our findings.

The patient demographics and baseline characteristics were analyzed. Patients' ages ranged widely, with a mean age of 65.92 ± 10.57 years, indicating the broad age range among the participants. The gender distribution was skewed towards males, accounting for 63.54% of the cohort, mirroring the higher incidence of gastric cancer in men than in women. The mean BMI was 24.43 kg/m^2, which falls within the healthy weight range per World Health Organization (WHO) guidelines, indicating that obesity did not substantially contribute to the health burden in our patient cohort.

The health status of the patients was also a significant focus of our study. A prominent finding was the moderate prevalence of comorbidities and concurrent medications. Hypertension was the most common comorbidity in 35.42% of patients, followed by malnutrition requiring nutritional support in 12.48% of patients and cardiovascular diseases (cerebral infarction, heart failure, chronic coronary disease) in 9.38%. The concurrent use of medications was frequent among our patients, with proton pump inhibitors being the most common, taken by 41.67%.

Our patient cohort's baseline laboratory results provided valuable insights into their initial health status before commencing the FLOT regimen. Key findings included a mild degree of renal dysfunction (mean eGFR at baseline was 85.69 mL/min/1.73 m^2 [SD ± 16.69], SCr level of 0.90 mg/dL [SD ± 0.21], serum urea level of 28.6 mg/dL [SD ± 13.5]), a modest degree of anemia (mean hemoglobin level of 12.68 g/dL [SD ± 1.87]), an average leukocyte count (mean white blood cell count of 7,451.04 cells/nm^3 [SD ± 1,831.80]) and normal electrolytes (mean serum calcium, sodium, and potassium levels of 9.22 mg/dL [SD ± 0.39], 140.55 mmol/L [SD ± 1.88], and 4.31 mmol/L [SD ± 0.48], respectively).

Incidence of AKD

Three patients developed AKD during the follow-up period, resulting in an incidence rate of 0.0104 cases per month of follow-up. Based on the Poisson distribution, the 95% confidence interval for the incidence rate ranged from 0.000 to 0.0243, suggesting a relatively low but non-negligible risk of AKD in this patient cohort (Table 4 and online suppl. Table 4; for all online suppl. material, see https://doi.org/10.1159/000545638). Mean eGFR remained stable over time (Fig. 1).

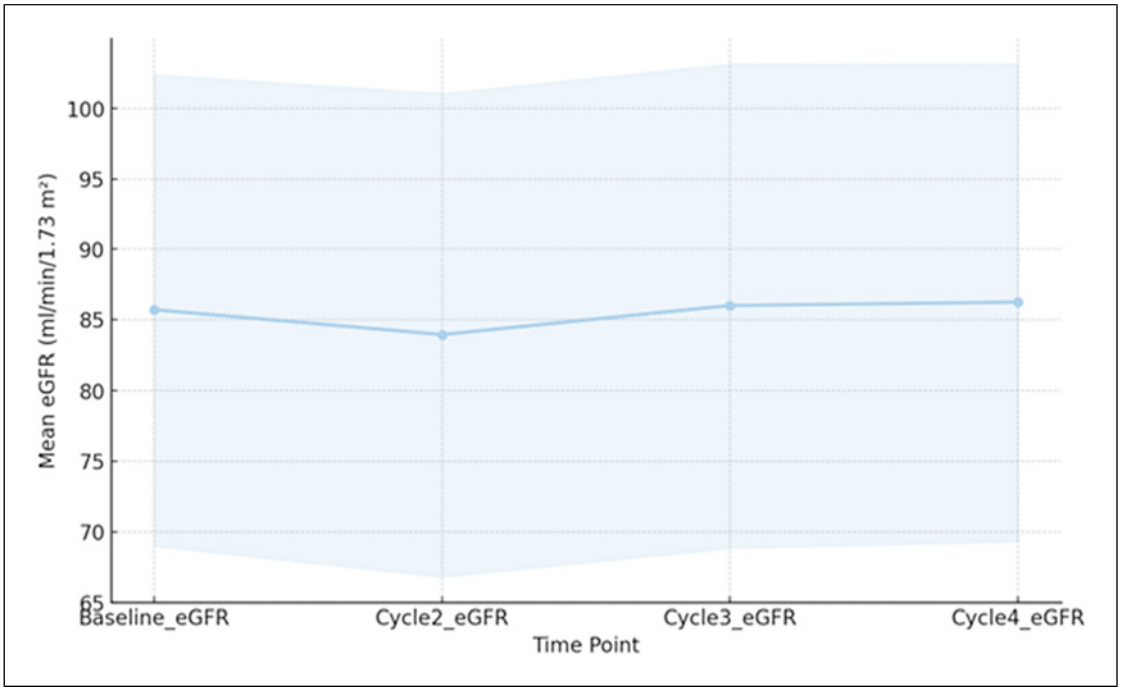

Fig. 1. Mean eGFR over time with standard deviation.

In all cases, the SCr increase was less than double the initial baseline level and promptly resolved after intravenous hydration. None of the patients required hemodialysis or intensive care unit admission due to renal complications.

Univariate and Multivariate Analysis

After adjusting for other factors in the model, two predictors remained significantly associated with the risk of AKD: the use of oral antidiabetic agents and the presence of benign prostatic hyperplasia. Oral antidiabetic agents emerged as a significant predictor of AKD (p value = 0.018). Diabetes is known to affect kidney function, and the additional burden of chemotherapy might potentially exacerbate this effect. Another significant predictor from the univariate analysis was benign prostatic hyperplasia (p value = 0.025) (Tables 5, 6). However, since the number of events was low, the risk of overestimation is concrete.

Table 5. Univariate analysis for continuous variables

Independent variable	p value	Odds ratio	95% CI
Age	0.227	1.095	[0.945, 1.269]
Height	0.128	0.899	[0.784, 1.031]
Weight	0.197	0.919	[0.808, 1.045]
Baseline urea	0.237	1.029	[0.982, 1.078]
Baseline hemoglobin	0.118	1.648	[0.881, 3.082]
Baseline WBC	0.025	1.001	[1.000, 1.001]
Baseline neutrophils	0.168	1.000	[1.000, 1.001]
Baseline lymphocytes	0.334	1.000	[1.000, 1.001]
Baseline calcium	0.461	2.990	[0.162, 55.013]
Baseline sodium	0.560	0.833	[0.450, 1.540]
Baseline potassium	0.678	0.694	[0.124, 3.892]
Baseline creatinine	0.017	0.000	[0.000, 0.205]

Discussion

This study aimed to explore the risk of AKD among gastric cancer patients undergoing the FLOT chemotherapy regimen and identify its potential risk factors. In oncological care, prioritizing the evaluation of AKD over AKI is fundamental. If global data underline that some patients may experience AKI due to the nephrotoxicity of FLOT, no studies focused on the AKD onset. This crucial event can affect both AKI patients and normal renal function ones that, after 7 days from the therapy, show a

Table 6. Univariate analysis for categorical variables

Independent variable	*p* value	Odds ratio	95% CI
Gender	0.909	0.868	[0.076, 9.927]
Diabetes	0.069	11.125	[0.825, 149.949]
Hypertension	0.282	3.813	[0.333, 43.666]
Smoker	0.805	1.360	[0.118, 15.663]
Alcohol	0.999	0.000	[0.000, inf]
Liver	1.000	0.000	[0.000, inf]
BPH	0.046	15.000	[1.047, 214.838]
Thrombophilia	0.998	0.000	[0.000, inf]
Malnutrition	0.999	0.000	[0.000, inf]
CVD	0.998	0.000	[0.000, inf]
RAAS inhibitors	0.299	3.727	[0.312, 44.579]
Beta blockers	1.000	0.000	[0.000, inf]
Calcium antagonist	0.158	6.143	[0.494, 76.426]
Diuretics	0.069	11.125	[0.825, 149.949]
ASA	1.000	0.000	[0.000, inf]
Oral antidiabetic agents	0.028	22.750	[1.412, 366.492]
Insulin	0.999	0.000	[0.000, inf]
PPI	0.767	0.692	[0.061, 7.907]
NSAIDS	1.000	0.000	[0.000, inf]

BPH, benign prostatic hyperplasia; CVD, cardiovascular disease; RAAS, renin angiotensin aldosterone system; ASA, acetylsalicylic acid; PPI, proton pump inhibitors; NSAIDS, non-steroidal anti-inflammatory drugs.

renal impairment. In our study, we intentionally chose not to emphasize the incidence of AKI among the patient cohort. Instead, we focused on AKD as a parameter as it provides more comprehensive information about the renal prognosis in the medium to long term. This approach helped us identify renal damage patterns even in cases where the damage occurred gradually and had a more insidious course, as was observed in our patient cohort.

In clinical practice, a laboratory mild increase of SCr (and a subsequent reduction of eGFR) in the immediate post-therapy window time could be related to the hydration status and a transitory biological event without real clinical relevance [23]. On the contrary, a persistent renal dysfunction after the AKI timeframe could be fundamental for the oncologists to decide how to proceed with the medical regimen, choosing a reduction of the drug dosage or a therapy interruption [24].

The significance of AKD is illuminated by the fact that non-recovery from an acute renal dysfunction has been associated with the onset of de novo CKD and heightened mortality [25]. The risk of patients with AKD progressing to de novo CKD is significantly higher than those who recover from AKI, with a hazard ratio (HR) of 2.21 for the development of de novo CKD for patients who progressed to AKD compared to those who had early AKI recovery. These patients have a significantly higher mortality risk with an HR of 1.2 compared to those who recover from an AKI episode. The timing of AKI recovery emerges as a pivotal determinant of patient outcomes; the first 2–3 weeks following an AKI episode represent a critical window where the risk for adverse effects increases most rapidly and where interventions are, therefore, most likely to reduce the risk of progression to CKD or early mortality [25]. Recognizing AKD in the early stages allows for more aggressive treatment, potentially curtailing adverse events and preventing the progression of AKD and the development of CKD [26].

Despite the small cohort size and low number of AKD events, our research unveiled valuable insights into the renal safety profile of FLOT. The incidence rate of AKD

was relatively low at 0.0104 cases per month of follow-up, indicating that the FLOT regimen is relatively safe for renal function. However, it is crucial to remember that our study's small sample size might have underestimated the incidence rate. Therefore, more extensive cohort studies with extended follow-up periods are needed to validate our findings further. Based on our univariate analysis, the use of oral antidiabetic agents and the presence of prostate hypertrophy are significant predictors of AKD. Even after adjusting for other factors, both conditions remained associated with AKD risk. However, due to the limited number of events, we cannot provide a clinical significance of these findings. These results should be analyzed in larger cohorts to understand their implications better.

The association between oxaliplatin exposure and renal toxicity has been previously reported. In a study by Da Silva Fernandes et al. [27] it was observed that 7.5% of patients treated with an oxaliplatin regimen for various solid malignancies developed renal toxicity. Their study also highlighted the need for closer monitoring and potential modification of treatment regimens to minimize renal impairment. Importantly, they suggested an increased focus on preventative strategies, such as adequate hydration and dose adjustments in patients with risk factors for renal impairment. This aligns with our study's observations, underscoring the relevance of a personalized hydration strategy approach in routine clinical practice.

Research by Takimoto and colleagues [28] conducted in non-small-cell lung cancer patients has highlighted the nephrotoxic potential of docetaxel, one of the drugs incorporated in the FLOT regimen[14]. Docetaxel has been associated with acute tubular nephrotoxicity due to interference with the transport of organic ions in the kidneys, leading to tubular damage. This can result in the leakage of specific low-molecular-weight peptides into the urine, biomarkers that can be utilized for diagnosing acute tubular nephrotoxicity and monitoring kidney damage progression. The risk appears higher in patients with pre-existing renal disease or those receiving repeated doses of docetaxel [28]. In our study population, the renal function was generally well maintained at baseline. This may have influenced our results as patients with better renal function at baseline might have been more resilient to the nephrotoxic effects of the FLOT regimen. However, despite this initial renal health, the short length of the FLOT treatment schedule and the mild impact of CKD may have contributed to the reduced docetaxel and oxaliplatin toxicity observed.

Our study has limitations that should be acknowledged. First, the small sample size and the low number of AKD events may have constrained our study's statistical power to identify additional potential risk factors for AKD. Second, another limitation of our study is the lack of systematic assessments of nutritional status before, during, and after chemotherapy. Although malnutrition and weight loss are known to impact treatment tolerance and overall outcomes in cancer patients, their direct effect on AKD development in this specific context remains uncertain. Considering that our cohort had relatively well-preserved baseline renal function and the incidence of AKD was low, it is improbable that fluctuations in nutrition significantly affected renal outcomes. Lastly, in our study population, the renal function was generally well maintained at baseline, with a mean eGFR of 85.6 mL/min/1.73 m^2. This could potentially limit the generalizability of our findings as we can hypothesize a higher rate of adverse events in patients with worse renal function. This study reflects real-world clinical practice, where CKD patients are frequently excluded from anticancer treatments. Therefore, further studies involving patients with a lower baseline eGFR are needed to fully understand the renal toxicity of the FLOT regimen in this patient subgroup.

The study has several strengths, such as using a comprehensive dataset from four high-volume medical centers in Italy, applying robust statistical analysis methods, and the generalizability of the results to real-world clinical practice. Our study is unique because it focuses on evaluating AKD, which provides a more comprehensive assessment than isolated AKI detections. This indicates that the FLOT regimen tends to accommodate our patients' kidneys with proper monitoring and supportive care. The low incidence of AKD highlights the safety of the FLOT regimen for our patient's kidneys. The rigorous approach of emphasizing AKD evaluation and its promising outcomes can be applied to other studies examining different drugs and varying baseline renal functions, thereby improving the comprehensiveness of renal safety assessments for oncological drug regimens.

Conclusions

Based on our study, it appears that the FLOT regimen is a safe treatment option for gastric cancer patients in terms of renal dysfunction. The incidence of AKD was found to be low, but it is still essential to monitor patients, especially those with diabetes, on oral hypoglycemic agents and prostate hypertrophy. This will help in detecting and preventing the development of AKD during treatment, which can lead to CKD over time. Given the promising results of our study, a possible research

roadmap might include involving a larger cohort with diverse demographics, including patients with lower baseline renal function, to validate initial findings. Furthermore, the studies should be aimed at establishing long-term monitoring protocols for renal function in patients undergoing FLOT, integrating preventive strategies for those identified at higher risk. Specific attention should be given to capturing long-term outcomes, focusing on anticancer treatment efficacy, renal function, the number of hospital admissions, and quality of life years after treatment completion. Early identification of AKD is crucial for proposing efficient and tolerable anticancer treatment to a higher number of patients. These data emphasize the need for integrated onco-nephrological care models that prioritize both oncological effectiveness and renal preservation, with early identification of AKD to improve anticancer treatment.

Statement of Ethics

This study was conducted retrospectively using de-identified patient data. According to local guidelines, ethical approval was not required for retrospective analyses of previously collected clinical data. All patients provided written informed consent before initiating anticancer therapy, allowing the use of their medical data for research purposes. Written informed consent was obtained from all participants before starting their anticancer treatment. This included their agreement to use their anonymized clinical data for research purposes. Since the study utilized retrospective data, no additional consent was necessary.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, methodology, and visualization: Matteo Floris, Andrea Angioi, and Francesco Trevisani. Investigation: Matteo Floris, Michele Ghidini, Nicole Liscia, Manuela Dettori, Nicola Lepori, Paola Testoni, and Marco Puzzoni. Supervision: Francesco Trevisani. Project administration: Francesco Trevisani, Cinque Alessandra, and Elena Mazza. Software and formal analysis: Andrea Angioi. Data curation: Matteo Floris and Andrea Angioi. Writing – original draft: Matteo Floris, Andrea Angioi, Nicole Liscia, and Francesco Trevisani. Writing – review and editing: Matteo Floris, Andrea Angioi, Nicole Liscia, Francesco Trevisani, Antonello Pani, Gianfranca Cabiddu, Mario Scartozzi, and Stefano Cascinu. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to patient privacy considerations. However, they can be made available upon reasonable request. Further inquiries can be directed to the corresponding authors.

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