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Intensive hydration protocols and heart failure-compatible signs and/or symptoms in cisplatin-treated cancer patients: a prospective observational cohort study.

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Abstract

Introduction:

Cisplatin-based chemotherapy requires intensive hydration protocols to prevent nephrotoxicity, involving rapid administration of large fluid volumes. The potential cardiovascular impact of hydration-associated fluid overload remains poorly characterized. This study aimed to determine the proportion of patients presenting signs and/or symptoms compatible with heart failure following these protocols and to explore associated factors.

Methods

A prospective, observational, single-center cohort study was conducted between January and December 2021 at Hospital Universitario Marqués de Valdecilla, Spain. Adult patients with solid tumors receiving cisplatin-based chemotherapy with intensive hydration were consecutively enrolled. The primary outcome - occurrence of at least one sign and/or symptom compatible with heart failure - was assessed through electronic health record review and a structured questionnaire. Exploratory multivariable logistic regression was performed to identify associated factors.

Results

Twenty-nine of 120 patients (24.17%) presented at least one sign and/or symptom compatible with heart failure, most frequently palpitations (10.00%), dyspnea (9.17%) and edema (9.17%). In the multivariable logistic regression model, age ≥ 70 years (adjusted OR 2.93; 95%CI 1.13–7.61; p = 0.027) and administered volume per 500 ml increment (adjusted OR 2.96; 95%CI 1.06–8.27; p = 0.038) showed statistically significant associations with the outcome. Prior ischemic heart disease showed an elevated but non-significant estimate (adjusted OR 3.90; p = 0.075).

Conclusion

Age ≥ 70 years and administered volume showed statistically significant associations with the main outcome. Findings are hypothesis-generating and do not establish a causal relationship between hydration and the observed manifestations. Larger prospective studies with objective cardiovascular assessment are needed to confirm these findings and to evaluate individualized hydration strategies.

1. Introduction

Cardiotoxicity in oncology patients encompasses a broad spectrum of cardiovascular disorders resulting from antineoplastic treatments, including heart failure (HF) [1, 2]. The risk of cardiotoxicity is increased by classical cardiovascular risk factors, pre-existing cardiac disease, and prior exposure to

chemotherapy or radiotherapy, among others [2]. HF affects approximately 1–2% of adults in developed countries, with prevalence exceeding 10% in those over 70 years of age, and continues to be associated with high morbidity and mortality [3–7].

Cardiovascular disease and cancer share multiple risk factors, including smoking, obesity, physical inactivity, alcohol consumption, and environmental exposures such as air pollution and organic contaminants [8, 9]. Furthermore, numerous antineoplastic treatments can produce cardiovascular toxicity, including ventricular dysfunction, HF, and arterial hypertension, among others [2, 10, 11]. This close interaction has driven the emergence of cardio-oncology as a discipline dedicated to the prevention, diagnosis, and management of cardiovascular complications associated with cancer and its therapies [1, 10, 12, 13]. Treatments with established cardiovascular impact include anthracyclines, anti-HER2 agents, certain tyrosine kinase inhibitors, alkylating agents, and thoracic radiotherapy [2, 10, 11]. However, most available evidence has focused on the direct cardiotoxic effects of these agents, while the potential cardiovascular impact of administration-related factors - such as fluid overload associated with intravenous hydration protocols - has received far less attention.

Cisplatin remains one of the most widely used cytotoxic agents across a range of solid tumors. Although direct cardiotoxicity is uncommon, nephrotoxicity represents one of its principal dose-limiting adverse effects [14]. To mitigate this risk, clinical guidelines recommend intensive hydration protocols aimed at maintaining adequate diuresis, typically requiring the administration of large intravenous fluid volumes over a short period of time [15]. In clinical practice, these hydration protocols are determined primarily by the cisplatin dose administered and the need to prevent nephrotoxicity, without systematically accounting for patient-specific variables that may affect tolerance to rapid volume expansion, such as age, cardiovascular functional reserve, or the presence of comorbidities [15, 16]. As a result, patients with markedly different clinical profiles routinely receive similar hydration strategies, despite potentially differing risks of volume overload-related complications. From a pathophysiological standpoint, the rapid administration of large fluid volumes could promote circulatory congestion and trigger signs and symptoms compatible with HF [17]. Nevertheless, the frequency with which such clinical manifestations occur following cisplatin-associated hydration protocols remains poorly understood, and the evidence identifying patients at higher risk is limited. Characterizing these patients would support the development of more individualized hydration strategies capable of preserving nephroprotective efficacy while minimizing the risk of fluid overload-related complications.

The primary objective of this study was to determine the proportion of patients presenting signs and/or symptoms compatible with HF following intensive hydration protocols associated with cisplatin-based chemotherapy regimens. Secondary objectives included evaluating the association between the occurrence of these clinical manifestations and a range of demographic, clinical, laboratory, and cardiovascular variables, with the aim of identifying potential associated factors.

2. Materials and Methods

2.1. Study design

A prospective, observational, single-center cohort study was conducted between January and December 2021 at Hospital Universitario Marques de Valdecilla (a tertiary referral hospital), Spain. The study is reported according to the STROBE recommendations for observational studies [18].

2.2. Inclusion and exclusion criteria

Adult patients (≥ 18 years) with a solid tumor diagnosis who received cisplatin-based chemotherapy with intensive hydration protocols at the study site during the study period were consecutively enrolled. Initially, only patients with non-small cell lung cancer were eligible. Given the decline in the number of cisplatin-eligible patients following the approval of immunotherapy as a first-line treatment for this indication during the recruitment period, and following approval of a protocol amendment by the Ethics Committee, inclusion criteria were expanded to encompass all solid tumor types treated with cisplatin. Treatment decisions were made independently of study participation, in accordance with routine clinical practice and established eligibility criteria for cisplatin-based therapy [19].

Patients under 18 years of age and those receiving cisplatin-compatible chemotherapy regimens within the framework of a clinical trial were excluded.

2.3. Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Participants were informed of the study objectives and procedures both verbally and in writing, and provided written informed consent prior to enrollment. Both the initial protocol and the amendment were approved by the Ethics Committee of Cantabria on December 22, 2020 (Ref: 2020.414) and May 18, 2021 (updated version), respectively. Personal data were processed in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 (General Data Protection Regulation), and its implementation in Spain through Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights [20, 21]. Participants were also informed of their right to withdraw from the study at any time without consequences.

2.4. Sample size

In the absence of prior studies specifically estimating the frequency of signs and/or symptoms compatible with HF following cisplatin-associated hydration protocols, no directly applicable reference estimate was available for the primary outcome. An expected frequency of 8.5% was pragmatically assumed, based on available data on HF in populations with increased cardiovascular risk [5, 22]. With a 95% confidence level and a precision of ± 5%, the estimated sample size was 120 patients. This calculation was performed to estimate the frequency of the primary outcome and was not based on statistical power requirements for the multivariable analysis.

2.5. Data collection

Data were collected following written informed consent and medical record review, through a structured clinical interview conducted during the patient's outpatient visit for chemotherapy administration. Each patient was enrolled at a single chemotherapy cycle - the one corresponding to the moment of study inclusion - and only data from that specific treatment session were recorded.

To detect the occurrence of signs and/or symptoms compatible with HF following hydration protocol administration, follow-up was conducted at two time points. First, during the 72 hours after treatment administration, through systematic review of the institutional electronic health record, capturing any primary care consultations, emergency department visits, hospitalizations, or other medical interventions related to signs and/or symptoms compatible with HF. Second, at the time of the next chemotherapy cycle (approximately three weeks later), a structured clinical evaluation was performed using a study-specific questionnaire covering the period between treatment administration and the next cycle visit.

The questionnaire was developed ad hoc by the research team based on the signs and symptoms of HF described in the European Society of Cardiology (ESC) clinical practice guidelines current at the time of the study [23] (Table 1). The outcome was defined as the occurrence of ≥ 1 sign and/or symptom compatible with HF identified through electronic health record review within the first 72 hours or through the follow-up questionnaire. No confirmation via cardiac biomarkers, echocardiography, or formal cardiology assessment was required; accordingly, the outcome represents a clinical signal compatible with HF rather than a confirmed HF diagnosis.

Table 1
Structured follow-up questionnaire for the detection of signs and symptoms suggestive of heart failure.

Questionnaire item	Compatible sign/symptom
Have you noticed swelling in your ankles?	Peripheral edema
Have you noticed a bluish discoloration of your lips?	Cyanosis
Have you had difficulty breathing? Have you felt more tired than usual when performing your daily activities?	Dyspnea
Have you needed to sleep with more pillows or in a more upright position?	Orthopnea
Have you woken up suddenly at night feeling short of breath and needing to sit up?	Paroxysmal nocturnal dyspnea
Have you felt palpitations or a faster-than-normal heartbeat?	Tachycardia
Healthcare utilization questions	
Have you needed medical attention?	
Have you visited your primary care center or the hospital emergency department?	
Have you taken any diuretic medication?	

Source: authors' elaboration based on the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [23].

To identify potential factors associated with the occurrence of signs and/or symptoms compatible with HF, demographic variables, cardiovascular risk factors, medical history, and prior exposure to potentially cardiotoxic treatments were recorded in accordance with ESC recommendations [2] (Online Resource 1). Cancer-related variables were also collected, including primary tumor site, histology, disease stage, treatment line, and chemotherapy cycle number, as well as baseline clinical status (ECOG performance status, cachexia, and asthenia), relevant laboratory parameters, and concomitant medications potentially related to cardiovascular or renal function. Regarding treatment received, characteristics of the cisplatin-associated hydration protocol were recorded, including total administered volume, infusion rate, and weight-adjusted infusion rate, as well as diuretic use during the session, concomitant radiotherapy administration, and other cytotoxic agents.

All study data were entered into a structured electronic database specifically designed for this study. Data were pseudonymized before analysis, and access to the database was restricted to members of the research team to ensure data confidentiality and integrity.

2.6. Data analysis

A descriptive analysis was performed for demographic, clinical, cardiovascular, oncological, and treatment- and hydration-related variables. Categorical variables were expressed as absolute frequencies and percentages; continuous variables were summarized using measures of central tendency and dispersion. The outcome variable was defined as the presence of at least one sign and/or symptom compatible with HF during the follow-up period. For the bivariable analysis, patients who experienced the outcome were compared with those who did not. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test, as appropriate, and continuous variables using non-parametric tests when indicated.

Univariable logistic regression models were subsequently fitted to evaluate the association between each study variable and the presence of signs and/or symptoms compatible with HF. Associations were expressed as odds ratios (OR) with 95% confidence intervals (95% CI). To explore potential age thresholds associated with the outcome, age was categorized using cutoffs of 65, 70, and 75 years. The 70-year cutoff, which showed the clearest signal in the exploratory analyses, was used in the multivariable model. Total administered volume was rescaled in 500 ml increments (VOL500), and weight-adjusted infusion rate in 0.01-unit increments, to facilitate interpretation of the corresponding odds ratios. An exploratory multivariable logistic regression model was constructed including age ≥ 70 years, prior ischemic heart disease, and administered volume per 500 ml increment. Variable selection was based on clinical relevance and signals observed in the univariable analyses, rather than on statistical significance alone. Additional models were evaluated focusing exclusively on hydration-related parameters, incorporating administered volume alongside infusion rate expressed in ml/min and adjusted for body weight. A potential modification of the effect of administered volume by age was explored through an interaction term between VOL500 and age ≥ 70 years. A sensitivity analysis was also performed excluding patients with prior ischemic heart disease, ventricular dysfunction, or arrhythmia, to assess the robustness of findings related to hydration parameters after removing patients with pre-existing cardiovascular disease potentially associated with greater baseline susceptibility to the outcome. Model discrimination was assessed using the area under the ROC curve (AUC), and a formal comparison of ROC curves across models was conducted. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Stata, version 15 (StataCorp LLC, College Station, TX, USA).

3. Results

3.1. Descriptive analysis

One hundred and twenty patients were enrolled, with a mean age of 62.94 years; 73.3% were male and 99.17% had an ECOG performance status of 0–1. The most prevalent cardiovascular comorbidities were hypertension (40.83%) and dyslipidemia (39.17%); eight patients (6.67%) had prior ischemic heart disease. Lung cancer was the most frequent primary tumor (65.00%), and 83.33% of patients had locally advanced or metastatic disease. The majority received cisplatin in combination with another cytotoxic agent (91.67%). Median total administered volume was 3,883 ml (IQR: 3,806.5-4,006.5), with a median

infusion rate of 11.70 ml/min (IQR: 10.76–12.68). Complete cohort and treatment characteristics are presented in the supplementary material (Online Resource 2). During follow-up, 29 patients (24.17%) presented ≥ 1 sign and/or symptom compatible with HF. The most frequent were palpitations (10.00%; n = 12), dyspnea (9.17%; n = 11), and edema (9.17%; n = 11), followed by orthopnea (3.33%; n = 4) and cyanosis (0.83%; n = 1). Twenty patients presented a single manifestation, seven presented two simultaneously, and two patients presented three simultaneously.

3.2. Unadjusted analyses

In the unadjusted analyses, most variables evaluated did not show statistically significant associations with the outcome. Patients aged ≥ 70 years presented a higher frequency of signs and/or symptoms compatible with HF than those under 70 years (37.93% vs. 19.78%; p = 0.047). Administered volume per 500 ml increment showed a non-statistically significant association (OR 2.41; p = 0.081). Complete results of the unadjusted analyses are presented in the supplementary material (Online Resource 3).

3.3. Multivariable logistic regression analysis

The exploratory multivariable model included age ≥ 70 years, prior ischemic heart disease, and administered volume per 500 ml increment. Variable selection was based on clinical relevance and signals observed in the univariable analyses. The overall model was statistically significant (p = 0.0135). Model results are presented in Table 2.

Table 2
Multivariable logistic regression analysis of factors associated with signs and/or symptoms compatible with heart failure.

Variable	Adjusted OR	95% CI	p-value
Age ≥ 70 years	2.93	1.13–7.61	0.027
Prior ischemic heart disease	3.90	0.87–17.40	0.075
Total volume administered, per 500 ml increase	2.96	1.06–8.27	0.038

OR: odds ratio; CI: confidence interval. The model included age ≥ 70 years, prior ischemic heart disease, and total volume administered per 500 ml increase. Given the exploratory nature of the analysis and the limited number of events, estimates should be interpreted with caution. Source: authors' elaboration.

In the exploratory multivariable model, age ≥ 70 years and administered volume per 500 ml increment showed statistically significant associations with the outcome, while prior ischemic heart disease showed an elevated but imprecise estimate that did not reach statistical significance (Table 2). Additional analyses did not show statistically significant associations in the model based exclusively on hydration parameters (overall p = 0.0999), in the interaction between volume and age ≥ 70 years (p = 0.267), or in the sensitivity analysis after excluding patients with prior ischemic heart disease, ventricular dysfunction, or arrhythmia (overall p = 0.103). No statistically significant differences were observed between the AUCs of the models evaluated (p = 0.494); the combined model yielded an AUC of 0.658.

4. Discussion

This study evaluated the occurrence of signs and/or symptoms compatible with HF following administration of the cisplatin-associated hydration protocol. A notable finding was that 24.17% of patients presented at least one sign and/or symptom compatible with HF after treatment administration. This frequency is clinically relevant as a signal in a cohort predominantly composed of patients with good baseline functional status (ECOG 0–1 in 99.17%). However, given the absence of objective diagnostic confirmation and a control group, these findings should be interpreted as clinical manifestations temporally associated with the post-treatment period, and their occurrence cannot be specifically attributed to the hydration protocol. The cardiotoxicity of antineoplastic treatments has been extensively studied, with evidence focused primarily on the direct effects of agents such as anthracyclines, anti-HER2 agents, and certain tyrosine kinase inhibitors [2, 10, 11]. Yet neither European [17] nor American [24] HF guidelines, nor the 2022 ESC cardio-oncology guidelines [10], nor cardiovascular toxicity position papers [2] address fluid overload from intensive hydration protocols associated with treatments such as cisplatin as a potential cardiovascular risk mechanism. Notably, despite this absence in the published literature, oncology teams already apply selection criteria in routine clinical practice to exclude patients considered at high cardiovascular risk from these treatments - reflecting an implicit recognition of the risk that has not yet found formal support in the scientific evidence. This study represents an original contribution to this poorly characterized complication.

These findings are particularly relevant in the context of the bidirectional relationship between cancer and HF, in which the presence of HF may compromise the continuity of antineoplastic treatment and cardiovascular disease represents a leading cause of non-oncological mortality in cancer survivors [1, 8, 10, 25].

Administered volume showed a statistically significant association with the outcome in the exploratory multivariable model. However, this association was not reproduced in models focused exclusively on hydration parameters or in the sensitivity analysis. Taken together, these results suggest a possible relationship between fluid load and manifestations compatible with HF, but their inconsistency across analyses, the limited discriminative capacity of the model, and the observational design preclude consideration of this association as a robust independent effect or the establishment of a causal relationship.

Age ≥ 70 years showed a statistically significant association with the outcome in the exploratory multivariable model, while prior ischemic heart disease showed an elevated but imprecise estimate, limited by the small number of patients with this antecedent. No consistent associations were identified with the remaining cardiovascular or oncological factors evaluated. The low frequency of certain exposures and cardiovascular antecedents limited statistical power to detect associations in these subgroups.

The signs and symptoms included in the questionnaire were selected based on the ESC guidelines [23]. However, manifestations such as dyspnea, fatigue, edema, and palpitations are non-specific and may be

related to the underlying cancer or its treatment [17, 26]. Accordingly, although their occurrence following hydration constitutes a clinical signal temporally associated with treatment, the results should not be interpreted as confirmed HF episodes. These findings support the value of exploring individualized cardiovascular assessment prior to intensive hydration protocols, particularly in older patients or those with pre-existing cardiovascular disease. In this regard, the comprehensive monitoring of these patients represents a clinical challenge requiring specialized resources not always available in routine practice [27]. However, the available data do not support recommending modifications to hydration volumes or the preventive use of diuretics. These strategies will need to be evaluated prospectively, addressing both their cardiovascular safety and their nephroprotective efficacy.

4.1. Limitations

This study has several limitations. First, its observational, single-center design without a control group precludes the establishment of causality or the specific attribution of observed manifestations to the hydration protocol. Second, the outcome was based on signs and/or symptoms compatible with HF without confirmation through biomarkers, echocardiography, or formal cardiology assessment, which may overestimate the frequency of clinically confirmed HF. Additionally, only a single session per patient was evaluated, and the ad hoc questionnaire had not been formally validated. The expansion of inclusion criteria during the recruitment period increased cohort heterogeneity. Finally, the limited number of outcome events (n = 29) reduced the precision and statistical power of the models, particularly for infrequent exposures and subgroup analyses. This limitation is especially relevant for ischemic heart disease, which was present in only eight patients; accordingly, the estimated association between this variable and the outcome should be interpreted with particular caution.

5. Conclusions

In this cohort, 24.17% of patients presented at least one sign and/or symptom compatible with HF during follow-up after cisplatin administration with intensive hydration. Age ≥ 70 years and administered volume showed statistically significant associations with the outcome in the exploratory multivariable model, while the estimate for ischemic heart disease was imprecise. These results should be considered hypothesis-generating and do not permit the establishment of causality or the confirmation of HF episodes. Larger prospective studies with objective diagnostic confirmation are needed to evaluate the relationship between hydration and cardiovascular manifestations and the potential of individualized hydration strategies.

Declarations

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