New insights in cardiotoxicity and heart failure.

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Abstract

Myocardial dysfunction and the subsequent development of symptoms and signs of heart failure, which has been usually referred as cardiotoxicity, is one of the problems in cancer treatment therapies, that has raised highest concerns. Despite the different ways in which different drugs may cause myocardial damage, anthracyclines are drugs applied to most solid tumors and to patients with oncohematological pathologies, where the risk of developing heart failure can be as high as 48%.

Keywords: Cardiotoxicity, Heart failure, Cardio-oncology.

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Introduction

Most of the already used therapies are combined and/or sequential, implying the risk of exposure to many drugs that can induce the development of heart failure during the evolution of the treatment. As an example, this applies to patients treated with monoclonal antibodies, mainly trastuzumab (widely used in approximately 25% of breast cancer cases), or in the case of alkylating agents used in patients with non-Hodgkin lymphoma or in the pre-transplant of bone marrow (especiallycyclophosphamide) [1-3].

The development of adverse cardiovascular effects may, in some cases, have an impact at the psychological level (depression), leading to another negative effect: the interruption of cancer treatment [4-7].

The importance of research on variables that can predict or detect subclinical cases of heart failure has led to the rise of troponin I as predictor of cardiotoxicity in treatments using anthracyclines, trastuzumab and a combination of these two [8-10]. Additionally, echocardiograms (a widely available method of diagnostics), also allows the early detection of ventricular function deterioration. In turn, this leads to the use of cardioprotective drugs, of easy and frequent use, having the possibility to reduce the adverse effects, helping to avoid the interruption of cancer treatment. These drugs are the betablockers and inhibitors of angiotensin converting enzyme [11-13].

Even though it is usual to hear about two types of cardiotoxicity (type I, or irreversible and type II, or reversible), they seem to overlap or not having their bounds so clearly defined [14]. In patients treated with anthracyclines (typical example of type I), accumulated doses is a key factor that has been proved to be related to the occurrence of heart failure, while in patients treated with monoclonal antibodies such as trastuzumab (the classical example of type II), there are so called "classical" variables related to cardiovascular risk, which have even helped to make validated risk scores used to evaluate the chance of developing heart failure before the beginning of thetreatment[15].

In this context, the risk profile of these patients in Argentina has not been clearlyestablished, nor the alternatives for their treatment.

Materials and Methods

The study considered real life cases, from different medical centers and with a retrospective approach, including patients already diagnosed with cancer or with oncohematological pathologies (or myeloproliferative syndrome)

It was carried out in three institutions: San Juan de Dios Hospital and Centro Médico Capital, both located in the city of La Plata and Private Medical Center El Castaño in the city of San Juan.

A total of 267 patients were evaluated between January 1st, 2018 and December 31st, 2019.

All cases were evaluated in the external consultation services of each institution, either of cardio-oncology, oncology or oncohematology. In relation to their base pathology, and according to the requests of each specialist doctor attending each case, complementary and routine methods were carried out (routine/specific blood tests, cardiac biomarkers prior to the beginning of oncological or oncohematological treatment, study of cardiac images, hemodynamic studies, etc).

Inclusion criteria

Age above 14 years old.

Oncological, of oncohematological patients about to initiate treatments using chemotherapy drugs.

Exclusion criteria

Heart failure already diagnosed before the treatment with chemotherapy drugs is initiated.

Significative structural cardiopathy already existent (moderate to severe deterioration of systolic functions, severe valvular disease, congenital heart disease).

Cardiac event resulting in heart failure as an epiphenomenon of itself, and not related to chemotherapy.

One or more of the following items associated with treatments using chemotherapy drugs were considered as heart failure:

Cardiomyopathy, with clear signs of reduction in overall fraction ejection values or associated to septal segment alterations.

Symptoms of heart failure according to Framingham criteria.

Signs of heart failure (third noise, tachycardia, or both).

Initial reduction of at least 5% in the fraction ejection ratios below 55% in patients with signs or symptoms of heart failure; or at least of 10% below the 55% in asymptomatic patients.

Main Objectives

Evaluate the incidence of heart failure (HF) in oncological cases observed in every day medical practice.

Assess the incidence of cardiovascular complications in oncological cases observed in every day medial practice.

Analyze the association of the different drugs used in cancer treatment with cardiovascular complications.

Secondary Objectives

Evaluate the survival of patients with cardiotoxicity (CTX) after 6 months of the date of diagnostics.

Statistical Analysis

Quantitative variables (data) are presented in tables of frequency and percentages, with their confidence intervals. For the statistical description of quantitative data, the following measures were used (according to their distribution): mean ± standard deviation, or median and interquartile range. The analysis of discrete variables was done by using contingency tables and that or continuous variables, thought t-tests or Kruskall Wallis for non-paired data, or even variance analysis (ANOVA), is it suited to each case. The p-value threshold for statistical significance was set at $p<0.05$. Calculations were done by means of Epi Info 7.2 and Stata/SE v13.0 .

Results and Discussion

Population (Población) o sample (Muestra)

As mentioned before, a total of 267 patients were covered by the study, with a predomination of the female sex, with an average age of 57 years (Figure 1).

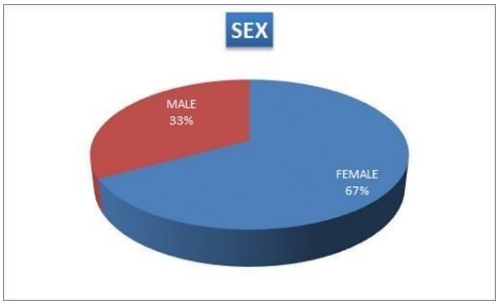

Figure 1. *Patients were covered by the study, with a predomination of the female sex.*

Considering population cardiovascular risk factors, one third were hypertense and, to a lesser extent, they were also heavy smokers, had dyslipidemia, were obese or showed documented heart disease (Figure 2).

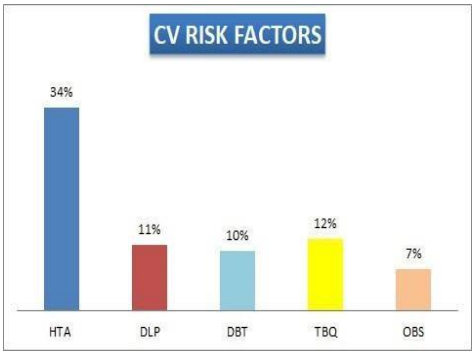

Figure 2. *Considering population cardiovascular risk factors, one third were hypertense.*

In the follow up process of this patients, 42 out of the 267, experienced adverse cardiovascular effects (15.7%), most of which were slightly or well tolerated (Table 1).

Table 1. *General Characteristic.*

Variable	N=267
Median Age (RIC 25-75%)	57 (47-66)
Sex femenin, %	67
Arterial Hypertension %	34
Diabetes melittus, %	11
Dislipemia, %	12
Tabaquism %	11
Obesity, %	7

Among those patients who developed CI (17), all of them presented ejection fraction (FEVI) before the treatment had begun, with an average of 62% ± 5.89. No patient showed a deterioration of this characteristic as long as symptoms of CI started to appear (Figure 3).

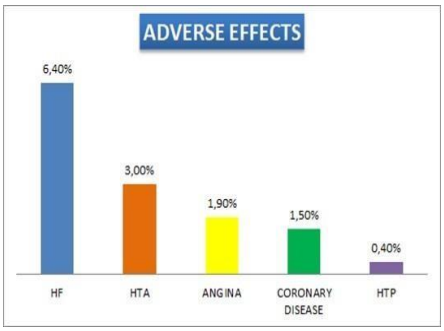

Figure 3. *Symptoms of CI started to appear.*

On the other hand, there was a sharp and distinctive difference among those patients experiencing CI, being more frequent in those with oncohematological problems, who are given the largest number of drugs in a simultaneous way.

Troponin dosage or BNP/NT Pro BNP basal was 1 out of every 5 patients under study.

Heart failure and its relationship with different drugs

Notoriously, being used alone in treatments (or without being associated to other cardiotoxic drugs), anthracyclines (AC) were not those which provoking the highest number CI cases. CI was instead more positively associated with alkylating agents (ALK), followed by monoclonal antibodies (MAB) and AC.

Another result is that when MAB and ALK are associated, the observance of CI is more notorious, being observed in nearly 1 out of 5 patients (Figure 4).

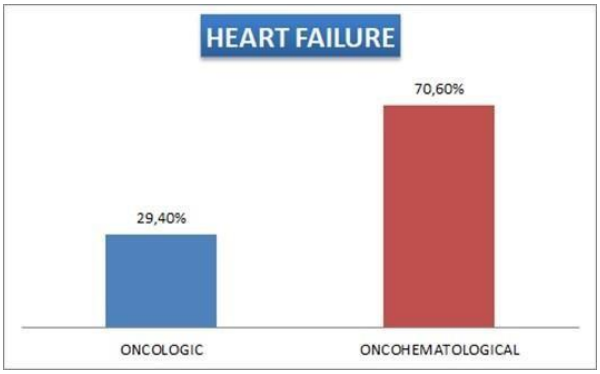

Figure 4. *The observance of CI is more notorious.*

Finally, it is worth mentioning that the use of immunotherapy did not show adverse cardiovascular effects, and that the study also excluded patients treated with antiproteasoma agents such as bortezomib or carfilzomib (Figure 5).

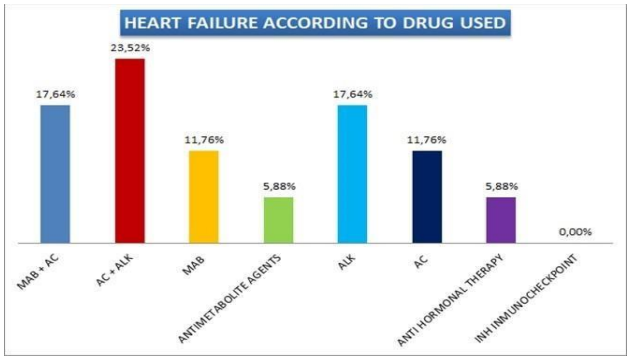

Figure 5. *The study also excluded patients treated with antiproteasoma agents.*

Antracyclines

A special note on AC: oncohematological patients are treated, with thehighest frequency, with AC, which adds to the frequency with which chemotherapy is applied, such as the cases of Non-Hodgkin's lymphoma and the well-known "R*CHOP" protocol (just to mention some of them). This may imply that it is likely that they have a higher risk of toxicity (Figure 6 and7).

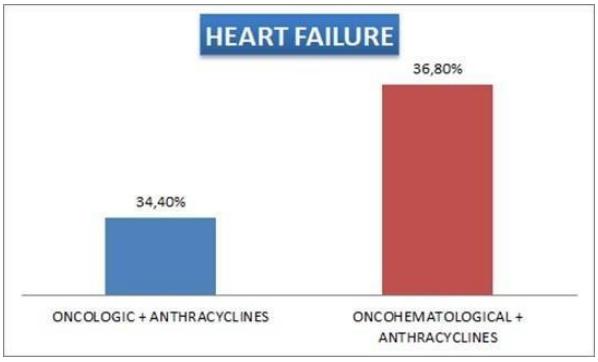

Figure 6. *This may imply that it is likely that they have a higher risk of toxicity.*

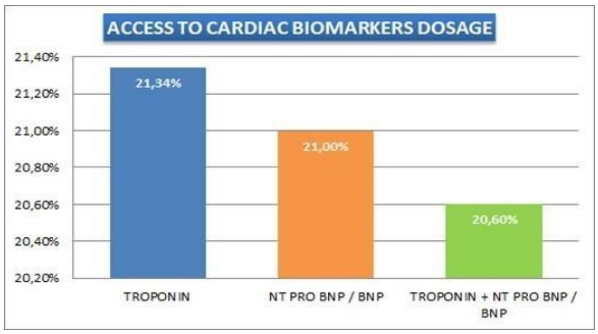

Figure 7. *This may imply that it is likely that they have a higher risk of toxicity.*

Mortality

In the six-month follow up process of the patients, none of those who developed adverse cardiovascular effects died. Registered mortality rate was 4.11% (11 patients).

Cardio-onco-hematology is an emerging discipline with special characteristics which include a close and continuous interaction between cardiologists, oncologists and oncohematologists.

A simple analysis or fear to a single drug has negative results in the majority of the cases, and in some occasions, it may deprive the patient of the chance of having "the best therapeutic option" in terms of risk-benefit. In the case of a patient with methodic evaluation and, eventually, with cardiologic protection, the previously mentioned argument could improve the therapeutic options, with a reduction in the probability of adverse effects.

CI is the most frequent adverse effect, but also tolerable and with specific treatments available according to medical knowledge. We have already mentioned thay while ALK and MAB may cause CI during the treatment, AC tend to cause after the treatment has finished. And we also know that taxane may cause bradycardia of first degree atrioventricular block in the first 72 hours (among other know effects).

The protocol to follow the evolution patients is still under discussion. This is due to the fact that guides based only and the use of drugs do not seem to consider the global situation of the patient, and a standardize follow-up process does not represent in a comprehensive way the medical craft required by the complexities of each case.

Patients under chemotherapy must have a proper basal cardiovascular assessment, which correctly estimates its cardiovascular risks in a multipara metric and individualized manner.

Any symptom should be overestimated so as to let future cardiomyopathy, or refractory hypertense patients go into treatment. Relying on figures of ejection fraction, in the context of image diagnostics such as transthoracic echocardiogram (with inter-observer variations of up to 10-15 points), leads us to fall into the most effective treatment selection bias. In the same way, the lack of a percentage reduction in the ejection fraction in asymptomatic patients leads to a lack of heart protection or to an inadequate treatment of the symptoms (wrong diagnostics of pneumonia or bronchitis).

In this context of polychemotherapy, multiple sequential treatments, the presence of pre-existent cardiovascular risk factors and the yet low awareness of adverse cardiovascular effects, we see ourselves in the need to continue working as hard as possible in attending these patients, so as to be able to find a balance between the right handling of their treatment, the efficient use of resources (both physical as well as humans), prevention and early treatment of cardiovascular problems.

Limitation of the Analysis

We must highlight the lack of resources for a comprehensive (integral) assessment of patients (biomarkers dosage, and use of modern techniques such as strain), as well as the shot follow up period (6 months), in the context of a patient population which usually have a low life expectancy.

Conclusion

An adequate local register of cardiotoxicity caused by chemotherapy drugs would strengthen the proper management of most common adverse effects, as well as different and individualized follow up protocols.

This step is unavoidable and will lead medicine to practical local guides not only based on drugs and their likely adverse effects. At the same time, building multidisciplinary units of cardio-onco-hematology is of the essence. And this, within each institution which deals with all the patients belonging to the population under risk.

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