Rev. Salud Pública. 22(3): 346-350, 2020

**Sección especial**
/ Special section

**Artículo / Investigación**
Article / Research

# Cardiotoxicity and cancer: prudential judgment in medical practice

## Cardiotoxicidad y cáncer: el juicio prudencial en la práctica médica

Juan C. García-Cruz, Edgar García-Cruz y Francisco M. Baranda-Tovar

Received 27th January 2020 / Send for modification 14th March 2020 / Accepted 30th May 2020


### ABSTRACT

The objective of this paper is to propose a conceptual tool for consideration by medical professionals and cardiologists, based on the concept of prudential judgment or *Aristotelian phronesis* to confront the problems of cardiotoxicity resulting from cancer treatments. We start by analyzing the case of a young female patient who received two types of therapies: the first with anthracyclines (adriamycin), which produces type I damage, as stated in the consensus of 2014; and the second treatment, one month later, with trastuzumab, an agent that produces type II damage not dependent on dose. In this case, the patient manifested acute cardiac insufficiency, with a decrease of LVEF to 28% on the echocardiogram and to 27% on magnetic resonance imaging. Reports have indicated that treatment with beta blockers and the suspension or decrease of the dose limits damage, but during preclinical stages. Awareness and early attention to subclinical damage have thus become extremely relevant to substantiate treatments based not only on clinical evidence but also on the ability of medical professionals to rely on prudential judgment, which moves away from the medical practices that are developed on a daily basis in order to influence and reduce the cases of irreversible heart failure known as cardiotoxicity.


**Key Words**: Cancer; ethics; judgment; professional competence; cardiotoxicity; drug therapy *(source: MeSH, NLM).*

JG: Bachelor in Communication and Journalism. M. Sc. Philosophy of Science (UNAM/Mexico). M. Sc. Philosophy, Science and Values (UPV/Spain), Ph. D. Philosophy of Science (UNAM/Mexico). CONACYT-Universidad Autónoma Metropolitana Xochimilco. Mexico City, Mexico.
*j.carlos.garcia.c@gmail.com*
EG: Medical Surgeon. Specialty in Internal Medicine, Subspecialty in Clinical Cardiology, High specialty in Intensive Cardiology Therapy, Echocardiography, Adult Congenital Heart Diseases (Spain). Instituto Nacional de Cardiología "Ignacio Chávez". Mexico City, Mexico.
*dr.edgar.gc@hotmail.com*
FB: General Medicine. Specialty in Internal Medicine, Subspecialty in Clinical Cardiology, Intensive Cardiovascular Therapy, Postgraduate in Heart Transplantation (Argentina), Heart Failure, and Transplants (Spain). Instituto Nacional de Cardiología "Ignacio Chávez". Mexico City, Mexico.
*francisco_baranda@yahoo.com.mx*


### RESUMEN

Este trabajo tiene como objetivo proponer el juicio prudencial o *phrónesis aristotélica* como herramienta conceptual para la deliberación de los profesionales de la medicina y cardiólogos para afrontar la problemática que implica la cardiotoxicidad como resultado de los tratamientos contra el cáncer. Partimos desde el análisis de caso de una paciente joven que recibió dos tipos de terapias: la primera con antraciclinas (adriamicina) que produce daño por el mecanismo tipo I, propuesto en el consenso del 2014, y un mes después con trastuzumab, agente que produce daño tipo II no dependiente de dosis. En este caso la paciente presentó insuficiencia cardiaca aguda, con disminución de la FEVI a 28% por ecocardiograma y de 27% por resonancia magnética cardiaca. Se ha reportado que el tratamiento con betabloqueadores y la suspensión o disminución de la dosis limita el daño cuando se encuentra en etapas preclínicas. Por ello el pensamiento y el abordaje temprano en búsqueda de daño subclínico ha tomado extrema relevancia para fundamentar los tratamientos no solo desde la evidencia clínica, sino también en el juicio prudencial que dejan las prácticas médicas desarrolladas día a día para impactar y reducir estos casos de falla cardiaca irreversible conocidos como cardiotoxicidad.


**Palabras Clave**: Cáncer; ética; juicio; competencia profesional; cardiotoxicidad; quimioterapia *(fuente: DeCS, BIREME).*

**DOI:** https://doi.org/10.15446/rsap.V22n3.84770

Cancer has one of the highest frequencies and mortality rates of any disease at the international level. It is the second most common cause of death: 8.8 million cancer deaths in 2015, and more than 18 million new cases and 9.6 million deaths in 2018 (1). The WHO predicts that due to changes in the birth rate and aging, by 2030, new cases will exceed 20 million per year (2). In recent years, the incidence of cancer has risen among people in the third and fourth decades of life.

The detection of cancer at an advanced stage and the lack of timely diagnosis and treatment are frequent problems that have increased adverse cardiological effects, both immediate and delayed, from cancer treatments; such effects range from cardiac insufficiency to coronary spasm, microvascular disease, ischemia originating in the epicardial coronary arteries, arterial hypertension, alterations in coagulation with arterial and venous thromboembolic events, pericardial or valvular disease, prolongation of the QT interval, and arrhythmias. Improved survival rates for cancer patients mean that we now have a population that suffers from chronic cardiological pathology (3).

This phenomenon was less evident in the past, since the life expectancy of cancer victims was sufficiently short to prevent the manifestation of chronic cardiovascular complications. At present, the risk of death from cardiovascular disease can surpass the risk of cancer recurrence (4, 5), and among children who survive cancer, death from heart disease can be even eight times higher (6). At the same time, the higher the age, the greater the effects of classic risk factors on cancer patients. Such clinical information has transformed cardiotoxicity resulting from oncological treatment (chemotherapy and radiotherapy) into one of the main complications of therapy; therefore, an interdisciplinary response will be increasingly necessary to ensure better management of a chronic population that is constantly growing.

The objective of this paper is to propose a conceptual tool for medical professionals and cardiologists to consider, from a perspective of the concept of prudential judgment or *Aristotelian phronesis*, to confront the problems implied by cardiotoxicity. The section following this introduction will describe the problem of cardiotoxicity in medical practice, especially the adverse effect of chemotherapy. The third section will discuss prudential judgment as a concept that seeks agreement and consensus to solve problems; we analyze the approach of *Aristotelian phronesis* and prudential judgment as a foundation for ethical decisions. In the fourth section, we address the case study of a young female patient who was diagnosed with cardiotoxicity in the early stage of treatment. We conclude with recommendations and results that may contribute to generating a fertile line of research investigation into cancer treatment from an interdisciplinary perspective.

## Cardiotoxicity in medical practice. An adverse effect of chemotherapy

In medicine and specifically in cancer treatment, ethical decisions have a fundamental social function. Deciding among a variety of novel treatment options and conventional possibilities can be a difficult task to assume. Making a selection, without ignoring the patient's dignity and autonomy, or rejecting medical and scientific integrity, can be an ethical dilemma. Ethics habitually appears when a choice must be made between two equally risky or difficult medical situations. Taking advantage of all the therapeutic possibilities offered by the scientific and technical development of medicine to save lives can be an obstacle, or can represent ongoing, stubborn aggression (7). In specific terms, cardiotoxicity derived from antineoplastic treatment is based on the degree of affectation of the left ventricular function. Therefore, the definition of cardiotoxicity can be based on the deterioration of the ejection fraction of the left ventricle (8), as presented in Table 1.

**Table 1**. Grades and consequences of cardiotoxicity

| Grades of Cardiotoxicity | Consequences |
|---|---|
| Grade I | Reduction of the ejection fraction from 10% to 20% with respect to the basal state. |
| Grade II | Reduction greater than 20% or to below normal (< 55%). |
| Grade III | Appearance of symptoms of congestive cardiac insufficiency and asymptomatic left ventricle dysfunction, in addition to toxic effects that can be expressed through the appearance of acute coronary syndrome, hypertension, thromboembolic phenomena, pericardiopathies, valvulopathies, arrhythmias, and alteration of the QT interval. |

The cardiovascular side effects of antineoplastic treatment must be added to the grades of toxicity. Ventricular dysfunction can be subdivided into two types: (7)

- Type I: Since the cardiotoxicity is produced by cell death, cardiac insufficiency can become manifest up to several years after the conclusion of antineoplastic treatment. It is dose dependent, implies a worse prognosis, and the medical paradigm is the anthracyclines.
- Type II: In this case, myocyte functioning is affected but the myocytes are not lost; thus ventricular dysfunction and cardiac insufficiency are reversible, without long-term aftereffects (7).

Cardiac dysfunction resulting from chemotherapy has been recognized since 1960. The time of LV dysfunction can vary by agent. In the case of the anthracyclines, damage is produced immediately after exposure (12). The

definition of myocardial damage, developed through consensus by the American Society of Echocardiography in 2014, mentions the following: decrease of LVEF >10 percentage points, to a value <53% and a decrease in the global longitudinal strain of more than 15% of the basal value. The guidelines of the European Society of Cardiology stipulate a decrease in LVEF to 50% and/or a decrease of more than 10% of LVEF with respect to the basal value (13,14). Use has also been made of biomarkers such as troponin and atrial natriuretic peptide. The current literature includes various definitions, but those mentioned above are still the most used.

As we can observe, the side effects of cardiotoxicity imply reflecting on the mechanisms of the adverse effects of drugs, which must be kept in mind when making decisions about suspending or continuing treatment. Prudence is needed when a difficult therapeutic decision requires choosing between potentially saving the cancer patient's life over the short and medium term and the possibility of long-term adverse effects that may affect the patient's prognosis. In such a situation, we believe that prudential judgment or *Aristotelian phronesis* can serve as a conceptual tool in making decisions based on scientific and medical evidence, while taking into account the experience and practices of the corresponding medical professional.

### *Aristotelian phronesis* and prudential judgment as the foundation for ethical decisions

Aristotle defined prudence as an "intellectual" virtue because of its relationship with knowledge and reason: Prudence is a formed faculty which apprehends truth by reasoning or calculation, and issues in action, in the field of human good […] It seems to be characteristic of a prudent man that he is able to deliberate well about what is good and expedient for himself, not with a view to some particular end, but with a view to well-being or living well (9).

Aristotelian thinking is coherent with the definition, since virtue is the means for man to become good. People achieve this through their daily actions, and such actions are good if they are in accordance with virtue: "… prudence is the willingness that enables people to deliberate correctly about what is good or bad for themselves (not as solitary beings, but within the world; not in general, but in a certain concrete situation), and to act, as a consequence, in a way that is useful" (10). Prudence understood in this manner has the function of selecting the adequate means for good deliberation, and therefore is a unique virtue; no other virtue can replace it. At first glance, prudent treatment could be a simple call for moderation and precaution in the form of reasoning employed for making decisions in concrete cases. We believe, however, that prudence is an indispensable element for correctly carrying out ordinary actions in which people intervene as rational beings, and even more so as ethical beings. Prudence has been considered so highly relevant for reflections on ethical discourse that philosophers of all eras have adopted it as a primary topic in their deliberations; they have assigned supremacy to prudence in the exercise of practical wisdom, viewing it as a virtue that aids in integrating all human actions with good aims. In other words, the application of prudence is required not as a science, but as a fundamental resource for all sensible action. Aristotle affirms: Prudence […] deals with human affairs, and with matters that admit deliberation, for the prudent man's special function, as we conceive it, is to deliberate well; but no one deliberates about what is invariable, or about matters in which there is not some end, in the sense of some realizable good. But a man is said to deliberate well (without any qualifying epithet) when he is able, by a process of reasoning or calculation, to arrive at what is best for man in matters of practice (9).

The prudent man possesses all virtues, and perfection is obtained through habitual usage; in other words, with practice. Aristotle alludes to virtues as personal, not as inherited or transmitted. People need the habit of reason because no good choice exists without wise deliberation based on practice. Correct judgment and the determination of action follow deliberation. The first two actions (deliberation and judgment) are theoretical and require the rule of will to become the determination of action. In that transition, a possible outcome is that, in spite of correct deliberation and judgment, the execution of action may fail. Prudence includes a certain art or skill to deal with each different or new situation. The reason, cleverness, and talent of a prudent person are needed to ensure a sensible and intelligent judgment. We believe that *phronesis* or prudence is practical wisdom. In other words, the level closest to the effective execution of *phronesis* is prudential judgment. As a result, the Greek term as well as the Latin *prudentia* are translated as the virtue of the prudent man. We must remember that wisdom, a practical ability, is directed at all times and is directly related to daily human activities, not only in intellectual deliberation but also in personal and family plans, as well as professional, social, and medical projects and activities where people perform action.

In this aspect, Gadamer attempts to clarify the concept of *phronesis* by returning to the Aristotelian distinction between science (*episteme*), *techné*, and practical wisdom (11). Aristotelian moral wisdom is not *episteme* or the theoretical knowledge of universal dimensions that are necessary for humans; in contrast, it deals with specific

contingent human actions, which are preceded by decisions and moral judgments not reached through inference. In addition, in the situation where we act, we cannot distance ourselves from any object; there is a horizon that includes us. According to this idea, we comprehend that human morality is distinct from nature. In human morality, it is not simply intellectual or habitual skills that have an effect, since people must use those skills to become unique individuals and behave as such. People develop their abilities and talents gradually. Gadamer argues that ethics are not measured as a mathematical or deductive phenomenon, but instead contain the essential traits of the individual who acts; in other words, the definition of a treatment does not result from human determination or action in the same way that the answer to a mathematical problem is solved by a mathematician (11).

Nonetheless, it is important to consider that individual maturity and education are elements that aid in determining the correct choice, while instructions given provide proof of individual attitude. Any rational action starts from the concrete: a philosophical reflection, a mathematical problem, or a social conflict, which all arise from individuals' interaction with their environment or the place of practice.

Therefore, we consider it pertinent to describe in the following section a case study that will exemplify the importance of prudential judgment or *phronesis* in medical practice, with reference to the cardiotoxicity provoked by cancer treatments.

**Case study**

The study begins with a female patient, aged 39, who detected two nodules in the upper quadrant of her left breast in October of 2014. The mammogram reported BIRADS 5 and the patient was referred to Mexico's Instituto Nacional de Cardiología, Ignacio Chavez. A biopsy showed infiltrating ductal adenocarcinoma and treatment was started with adriamycin and cyclophosphamide (4 cycles). In November of 2014, partial response to the treatment was determined (with a 50% decrease in tumor volume). An echocardiogram was reported normal: an ejection fraction of (LVEF) 66%, SGL -21%. In December of 2014, treatment began with paclitaxel/trastuzumab. The patient experienced heart failure in January of 2015, and requested emergency room assistance. The echocardiogram reported LVEF 28%, SGL -10% without cavity dilation. Magnetic resonance imaging reported LVEF 27% without cavity dilation. The patient received two types of therapy: the first with anthracyclines (adriamycin), which produces damages through mechanism type 1 described in the consensus of 2014; and the second, one month later, with trastuzumab, an agent that produces type II damage that is not dose dependent. In this case, the patient visited the emergency room with acute cardiac insufficiency, with a drop in LVEF shown as 28% on the echocardiogram and 27% on magnetic resonance imaging. Reports have indicated that treatment with beta blockers and suspending or decreasing the dose limits damage, but in preclinical stages. For this reason, early consideration and attention to subclinical damage has become extremely relevant. The objective is to reduce such cases of irreversible heart failure.

We are aware that the main treatment goal for any illness is to reestablish health and that the principle that all physicians follow is to cure the patient. However, aggressive illnesses like cancer require aggressive treatments that can cause severe complications. The physician must carry out a detailed analysis of each treatment employed, to contemplate the patient's circumstances and characteristics and the availability of multiple novel treatments. In this case, it is evident that the chemotherapy caused the patient's cardiotoxicity. We suggest, from medical practice, that before chemotherapy treatment begins, a basal echocardiogram should be done, along with another at the end of treatment or at the conclusion of the first phase of treatment, to establish if the chemotherapy caused the cardiotoxicity and thus consider treatment modification based on a risk/benefit analysis.

Such situations will be faced by many oncologists, since a suspension in treatment can accelerate cancer growth or cause a relapse, while continued treatment can lead to cardiac insufficiency. Medicine's fundamental principle of "first, do no harm" is at times taken to the limit with cancer patients, since their idiosyncratic response to treatment, in spite of necessary precautions, cannot be controlled. Therefore, we must rely on prudential judgments, which can take advantage of the medical practice of other colleagues to reach better decisions for addressing individual patient problems.

As a preliminary conclusion, we must take into account that risk factors for cardiotoxicity are associated with each type of cancer. Damage can be limited. Therefore, it is indispensable to rely not only on algorithms to evaluate risk versus benefit if a patient manifests damage from chemotherapy yet needs to continue treatment; on the contrary, we must promote sensible actions that are the result of a series of prudential judgments developed in medical practice during the search for practical reasons.

We define a sensible action as an action that can be justified, that could be accepted as reasonable by a person hearing an argument in its favor. The concept of practical reason assumes that in general, we can explain to others the reason why we act in a certain manner. In this sense,

it is pertinent to understand that *phronesis* is applied to unique situations; in the case at hand, the evidence obtained from medical practices allows decision-makers to reach the most appropriate prudential judgment. The case study also shows the existence of two types of solutions or alternatives to counteract the cancer and the cardiotoxicity. The first option is more problematic for the patient than the second. Nonetheless, the decision and the results depend on a consensus among the involved medical professionals and the patient, in addition to the physician's opinion, which will permit identifying more effective options based on the evidence and on medical practice. Such identification corresponds to accepting one's self as a person, as well as what one is able to do. "The adjective, 'responsible', can complement a wide variety of things: you are responsible for the consequences of your acts, but also responsible for others' actions to the extent that they were done under your charge or care" (15).

Because of the above, specialized services must be offered in hospitals that treat cancer patients. The multidisciplinary team must include the services of oncology, hematology, cardiology, echocardiography, radiology, imaging, and other disciplines such as philosophy and epistemology, which encourage operative, prudential concepts in medical practices. Evaluation must be made before, during, and after treatment, and guidelines established to stratify risk, prevention, treatment, the management of complications, and cardiac rehabilitation ♠

***Conflict of interest***: None.

## REFERENCES

1. IARC. Latest Global Cancer Data: Cancer Burden Rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. 2018 [cited 2019 Dec 1]. Available from: https://bit.ly/2CpbgTl.
2. OMS. Nota descriptiva: "Cáncer" [Internet]. 2018 [cited 2019 Dec 1]. Available from: https://bit.ly/3ffcLlz.
3. Sociedad Argentina de Cardiología. Consenso de diagnóstico, prevención y tratamiento de la cardiotoxicidad por tratamiento médico del cáncer. Revista Argentina de Cardiología. 81(5). Available from: https://bit.ly/3gFKV2m.
4. Yeh ET. Cardiotoxicity induced by chemotherapy and antibody therapy. Annu Rev Med. 2006; 57: 485-98. DOI: 10.1146/annurev.med.57.121304.131240.
5. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH. Overall survival and cause-specific mortality of patients with stage T1a, bN0M0 breast carcinoma. J Clin Oncol. 2007; 25: 4952-60. DOI: 10.1200/JCO.2006.08.0499.
6. Mertens AC, Yasul Y, Neglia JP. Late mortality experience in five year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol. 2001;19:3163-72. DOI: 10.1200/JCO.2001.19.13.3163.
7. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010; 102:14-25. DOI: 10.1093/jnci/djp440.
8. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005; 23: 2900-2. DOI: 10.1200/JCO.2005.05.827.
9. Aristóteles. Ética Nicomáquea. Madrid: Gredos; 2003.
10. Comte-Sponville, André. Pequeño tratado de las grandes virtudes. Barcelona: Ediciones Paidós Ibérica, S.A.; 2005.
11. Gadamer HG. Verdad y Método. Salamanca: Sígueme; 2005.
12. Shalkey V, Lenihan D, Ky B. Cancer Therapy–Induced Cardiotoxicity: Basic Mechanisms and Potential Cardioprotective Therapies. J Am Heart Assoc. 2014; 3(2):e000665. DOI: 10.1161/JAHA.113.000665.
13. Tromp J, Steggink LC, Van Veldhuisen DJ, Gietema JA, van der Meer P. Cardio-oncology: progress in diagnosis and treatment of cardiac dysfunction, Clinical pharmacology & therapeutics. 2017; 101(4):481-90.
14. Zamorano JL, Lancelloti P, Rodriguez D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). European Hearth Journal, 2016; 37(36):2768-2801. DOI: 10.1093/eurheartj/ehw211.
15. Ricoeur P. Sí mismo como otro. Madrid: Siglo XXI Editores; 2003.