

The lawsuits to antineoplastic drugs: the tip of an iceberg?

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Abstract *The lawsuits with antineoplastic drugs generate high costs for governments and require careful analysis to ensure efficient and adequate health results. This study analyzed cases conducted by federal entities to a reference institute for the treatment of cancer for technical opinion. Data were collected from copies of the cases examined from July 1 to December 31, 2013. It was analyzed: therapeutic subgroups, presence in essential drug list, drug registry, off-label use, indications of clinical practice guidelines, drug incorporation in Brazilian Health System and estimated value of court cases. 158 cases were examined, with a total of 164 requests of 35 antineoplastic drugs. Most of the medications were protein kinase inhibitors (31.4%), ten (28.6%) were included in the essential drugs list, three did not contain sanitary registration, ten had indication of off-label use, 56.7% were described in clinical practice guidelines and four drugs were recommended for incorporation. The total estimated amount of the court cases was R\$ 18,110,504.89. It was identified that the technical and sanitary instruments currently available to support the decisions seem to be insufficient and that there is need to establish strategies to minimize inconsistencies that compromise the comprehensiveness of care.*

Key words *Right to health, Antineoplastic, Judicial decisions*

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Introduction

The term “judicialization of health” refers to requests made to the judiciary related to health needs (access to services and products), at an individual or a collective level, that are not being met by the executive power¹. Oncology stands out among health care fields due to the number and the costs of related lawsuits. This phenomenon has been explained by the complexity of the technology used, the high cost involved, and the difficulties in accessing treatments and cancer care services²⁻⁴.

The right to access medicines has been one of the main requests presented in Brazilian courts⁴. This phenomenon has been observed in other Latin America countries, even when the universal right to health is not explicitly stated in their constitutions, as in the case of Peru, Argentina, Venezuela, and Ecuador⁵. The lawsuits related to antineoplastic drugs generate high costs for governments and demand detailed analyses to ensure an efficient use of public resources and positive outcomes for the health of citizens².

The following criteria are regarded as essential in analyses for decision making related to the supply of medicines via judicial means: technical analysis, identification of medicine registration with its respective indication within the Brazilian National Health Surveillance Agency (Anvisa - Agência Nacional de Vigilância Sanitária), available information in clinical guidelines, medicine availability/incorporation in the health system, identification of the drug in relation to essential medicines⁶. The use of these parameters appears to be essential to ensure the efficacy, accuracy, effectiveness, and safety of the medicines, to minimize unequal access to these medicines, and to endorse the integrality of the pharmaceutical services.

However, the current pharmaceutical services model of the Brazilian Public Health System (SUS – Sistema Único de Saúde), with its basic, strategic, and specialized components, does not include the supply of oncological medicines⁷. In addition, a single list of antineoplastic medicines is lacking in the public health system, there are no specific funds for these medicines, and the clinical guidelines for oncology include only some cancer types. Are these the motivating factors for the large number of lawsuits related to antineoplastic medicines observed in Brazil? Are the lawsuits the tip of an iceberg that is a warning about the need for a better understanding of the complexity of the oncological pharmaceutical services in the country?

In this context, the present study aimed to analyze the lawsuits involving the provision of antineoplastic drugs lodged against federal entities that had been evaluated by the National Cancer Institute José Alencar Gomes da Silva (INCa – Instituto Nacional de Câncer José Alencar Gomes da Silva) between July and December 2013. The goal was to deepen the understanding about the complexity of oncological care and its interfaces with pharmaceutical services.

Method

This was an exploratory study using a quantitative approach based on records of lawsuits lodged against the federal government, states and/or municipalities, referred by these entities to the INCa for the issuing of a technical opinion. Data were collected from lawsuits analyzed by the institute from July 01 to December 31 of 2013.

The primary source of information was a copy of the judicial process, provided by several justice courts throughout the country. Only the processes that had a technical report issued by the institutional division of regulation and technical standards and that were related to antineoplastic medicines were included in the study. Processes in which the purposes were exclusively the supply of support medicines for cancer treatment, other health supplies, or access to services, such as surgery or radiotherapy, were excluded.

The collected data were systematized using the *Microsoft Excel*® software (2010 version), which was also used for the descriptive analyses of data.

The following five indicators adapted from Pepe *et al.*⁸ were used: (i) proportion of medicines per therapeutic/pharmacological/chemical substance subgroup; (ii) proportion of required medicines included in the list of essential medicines from the World Health Organization (WHO)⁹; (iii) proportion of medicines registered within Anvisa; (iv) proportion of lawsuits with at least one medicine prescribed for off-label use; (v) proportion of therapeutic indications included in the Brazilian Clinical Protocol and Therapeutic Guidelines for Oncology (PCDT-Onco – Protocolos Clínicos e Diretrizes Terapêuticas em Oncologia)¹⁰. In addition, the study also pursued to confirm that the Brazilian National Committee for Health Technology Incorporation (Conitec – Comissão Nacional de Incorporação de Tecnologias) recommended that the requested medicines be incorporated in the SUS and to estimate the cost of the analyzed lawsuits.

The therapeutic subgroups were categorized according to the Anatomical Therapeutic Chemical system (ATC) proposed by the WHO (http://www.whocc.no/atc_ddd_index/). The decision to use the list of essential medicines from the WHO was based on the fact that antineoplastic drugs are not included in the Brazilian list of essential medicines (Rename – Relação Nacional de Medicamentos Essenciais)¹¹. To identify the medicine registration, a search was carried out in the Anvisa website, (http://www7.anvisa.gov.br/datavisa/consulta_produto/Medicamentos/frm-ConsultaMedicamentos.asp). The medicine information leaflets available at the Anvisa website (http://www.anvisa.gov.br/datavisa/fila_bula/index.asp) were accessed to identify discrepancies between the indication of use of a specific product and the information in the leaflet, thus characterizing off-label use.

The recommendation for use of the medication as Clinical Protocol and Therapeutic Guidelines (PCDT – Protocolos Clínicos e Diretrizes Terapêuticas) or as Diagnostic and Therapeutic Guidelines (DDT – Diretriz Diagnósticas e Terapêutica) was verified in the Brazilian PCDT-Onco. The protocols establish criteria for diagnosis, as well as parameters and standards for the use of a specific technology for a particular disease or condition. DDTs are used to indicate what is technically and scientifically valid when standardization of attitudes is not possible because of the variability of possible interventions¹². The website of Conitec (<http://conitec.gov.br/>) was accessed to verify if the medicines had been recommended for incorporation.

The monetary amounts for treatments indicated in the processes were considered to calculate the amounts of the lawsuits. When information about these amounts were not available, the calculation was based on the lowest value of the maximum price set by the government outlined in the table of the Medicine's Market Regulation Chamber (CMED - Câmara de Regulação do Mercado de Medicamentos) of Anvisa (<http://portal.anvisa.gov.br/listas-de-precos>) for 2013, and on data from the medical prescription available in the process. The mean values of the lawsuits were also estimated for each medicine to identify the most expensive ones.

This study was submitted and approved by the Research Ethics Committee (CEP – Comitê de Ética em Pesquisa). In accordance with current regulations, the information was compiled in a way that none of the persons could be identified.

Results

A total of 274 processes were identified, of which 215 (78.5%) involved some type of medicine, 20 (7.3%) involved diagnostic exams, 17 (6.2%) requested surgical procedures, 11 (4.0%) requested access to services; five (1.8%) requested radiotherapy, and six (2.2%) requested other procedures.

Fifty-seven of the 215 processes involving medicines were excluded because they were related to support drugs in cancer treatment. Thus, 158 processes involving 164 requests of 35 types of medicines were included, as demonstrated in Table 1.

Graph 1 shows the proportion of medicines requested per therapeutic subgroup. This indicator showed that the highest proportion was related to the protein kinase inhibitor subgroup (31.4%), followed by the monoclonal antibody subgroup (17.1%).

Of the 35 requested medicines, ten (28.6%) appeared, at least as one of the indications, in the list of essential medicines of the WHO. Of the 60 requested indications, 13 appeared in the list (Chart 1).

It was observed that 91.4% of the medicines requested by legal means were registered with Anvisa. Three medicines had no sanitary registration at the time of the analysis: lenalidomide, nelarabine, and regorafenib.

Regarding off-label use, 3.8% of the lawsuits had at least one medicine prescribed for use with no description in the medicine information leaflet. The eight medicines and the ten indications of off-label use are presented in Chart 1.

The analysis of the proportion of therapeutic indications listed in the PCDT-Onco showed that 56.7% were described as PCDT or DDT. It was observed that four medicines, for six indications, had been recommended by Conitec to be incorporated in the SUS. Chart 2 presents the therapeutic indications that appear in the PCDT-Onco and the medicines requested in the analyzed lawsuits (with their respective indications) whose incorporation in the SUS was recommended by Conitec.

The total estimated amount of the analyzed lawsuits was R\$ 18,110,504.89 (Brazilian money). This amount does not include the estimated amount of the judicial process involving nelarabine, because this financial information was not available in the analyzed documents and the CMED did not have an established price for this medicine in 2013. The mean estimated value of

Table 1. Classification, according to ATC*, of antineoplastic drugs requested in lawsuits analyzed by the National Cancer Institute José Alencar Gomes da Silva, between July and December 2013.

Drug	ATC*	Number of requests	Frequency (%)
Abiraterone	L02BX03	3	1.8
Anastrozole	L02BG03	1	0.6
Azacitidine	L01BC07	1	0.6
Bevacizumab	L01XC07	12	7.3
Bortezomib	L01XX32	1	0.6
Capecitabine	L01BC06	2	1.2
Cetuximab	L01XC06	20	12.2
Cisplatin	L01XA01	1	0.6
Decitabine	L01BC08	1	0.6
Erlotinib	L01XE03	6	3.7
Everolimus	L01XE10	5	3.0
Exemestane	L02BG06	1	0.6
Fludarabine	L01BB05	2	1.2
Fotemustine	L01AD05	1	0.6
Gefitinib	L01XE02	3	1.8
Goserelin	L02AE03	1	0.6
Imatinib	L01XE01	2	1.2
Ipilimumab	L01XC11	3	1.8
Lapatinib	L01XE07	3	1.8
Lenalidomide	L04AX04	1	0.6
Nelarabine	L01BB07	1	0.6
Oxaliplatin	L01XA03	1	0.6
Paclitaxel	L01CD01	1	0.6
Panitumumab	L01XC08	2	1.2
Pazopanib	L01XE11	5	3.0
Pemetrexed	L01BA04	2	1.2
Regorafenib	L01XE21	1	0.6
Rituximab	L01XC02	38	23.2
Sorafenib	L01XE05	7	4.3
Sunitinib	L01XE04	24	14.6
Tamoxifen	L02BA01	1	0.6
Temozolamide	L01AX03	3	1.8
Temsirolimus	L01XE09	2	1.2
Trastuzumab	L01XC03	3	1.8
Vemurafenib	L01XE15	1	0.6
Total		164	100.0

* ATC: Anatomical Therapeutic Chemical.

the processes was R\$ 222,582.88, which ranged from R\$ 2,032.41 to R\$ 613,044.84.

The calculation of the mean value per medicine showed that the ten most expensive medicines were the following: lenalidomide (R\$ 261,360.00), lapatinib (R\$ 230,077.30), regorafenib (R\$ 197,000.00), decitabine (R\$ 193,577.60), ipilimumab (R\$ 193,333.00), panitumumab

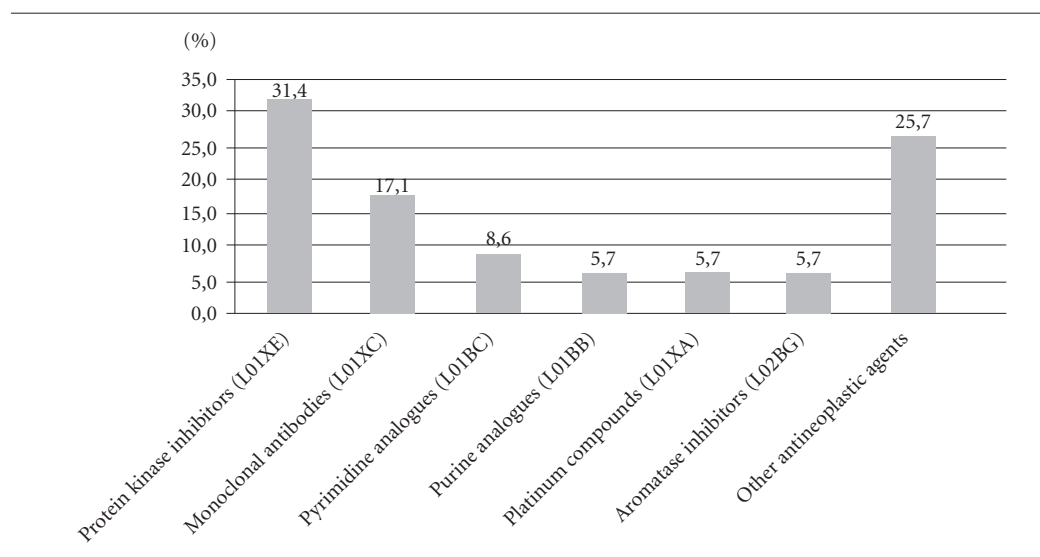
(R\$ 175,483.74), imatinib (R\$ 170,676.18), trastuzumab (R\$ 155,875.00), sunitinib (R\$ 148,728.77), and fotemustine (R\$ 144,935.56).

Discussion

This study showed that the majority of the lawsuits in the field of oncology involve pharmacotherapy (78.5%) and that the technical sanitary tools currently available to support decisions related to oncological medicines seem to be insufficient. The high number of requests of medicines put forward by individuals via the judiciary indicates difficulties to access health services, sanitary gaps, and outdated available technologies¹³⁻¹⁵. However, the present study shows other aspects that demonstrate a level of disarticulation between the pharmaceutical services and the oncological assistance models.

The analysis of medicines by therapeutic subgroups showed that the greatest proportion of requested medicines refers to the protein kinase inhibitors (31.4%) and that the proportion of monoclonal antibodies was 48.7% of the requests analyzed by the INCa. The increasing level of technological innovation in the area of health, including pharmacological technologies, has allowed expanding the number of alternatives for prevention and treatment of diseases¹⁶. The technological advances, especially those related to biotechnologically developed medicines (such as monoclonal antibodies) and target-specific drugs (such as protein kinase inhibitors), have allowed the introduction of a variety of new treatments in oncology¹⁷⁻¹⁸. However, these innovations have also been widely pointed out in the literature as one of the main causes for the accelerated increase in the costs of oncological care worldwide¹⁹⁻²¹. A study by Brunnel²² warned that 90% of all antineoplastic drugs approved by the Food and Drug Administration (FDA) for use in the USA cost more than US\$ 20,000 for a 12-week treatment. Fojo and Grady²⁰ expanded the discussion by warning about the association of few clinical benefits when compared to the high costs related to the treatment of cancer, mainly leveraged by the introduction of biotechnology drugs. The current funding system for oncological treatments that uses payment per procedure⁷, which usually does not provide sufficient amounts to cover the costs of innovative medicines, may lead to lawsuits.

The use of the list of essential medicines of the WHO showed that 21.7% of the indications



Graph 1. Proportion, by therapeutic subgroups, of medicines requested in lawsuits analyzed by the National Cancer Institute José Alencar Gomes da Silva, between July and December 2013.

Chart 1. Medicines and their respective therapeutic indications cited in lawsuits analyzed by the National Cancer Institute José Alencar Gomes da Silva, as referred in the list of essential medicines of the WHO and off-label indication.

Medicines included in the list of essential medicines of the WHO	
Anastrozol	Breast
Capecitabine	Breast
Cisplatin	Lung
Fludarabine	Chronic Lymphocytic Leukemia
Imatinib	Gastrointestinal Stromal Tumor Chronic Myeloid Leukemia
Oxaliplatin	Metastatic colon
Paclitaxel	Breast
Rituximab	Non-Hodgkin's Follicular Lymphoma Diffuse Large B-cell Lymphoma Non-Hodgkin's Lymphoma (not specified)
Tamoxifen	Breast
Trastuzumab	Breast
Medicines with off-label use request	
Bevacizumab	Brain
Cisplatin	Lung
Erlotinib	Breast
Exemestane	Breast
Lenalidomide	Multiple Myeloma
Nelarabine	Hodgkin Lymphoma
Regorafenib	Metastatic colon
Rituximab	Chronic Lymphocytic Leukemia Non-Hodgkin's Mantle Cell Lymphoma Thyroid

for the requested drugs appeared in the document and that relevant technologies are not being adequately offered to the population. The lack of antineoplastic medicines in the Rename is an important issue because it hinders a detailed analysis for decision-making in the case of a lawsuit. The list of essential medicines is an important and defining instrument to organize pharmaceutical services and to ensure access to drugs that are essential to meet the needs of a population²³. This gap in Rename compromises the prescription, dispensing, and safe and appropriate use of antineoplastic drugs²⁴. In addition, it limits access and promotes inequities regarding cancer therapeutics, thus opposing the assumptions stated in the description of integral therapeutic assistance of the SUS, foreseen in the Decree-Law no. 7.508/2011²⁵.

As far as requests of medicines without an Anvisa registration are concerned, it should be highlighted that their provision can endanger the patient's safety⁶. This was a topic of recent debates at the highest entity of the Brazilian judiciary²⁶. The proposal currently under discussion foresees that the public power will only be obliged to pay for an expensive medicine that has not been incorporated to the SUS and has been requested by legal means if the medicine has an Anvisa registration. This proposal is based on the fact that the provision of a non-registered drug represents risks for the patient, as there is no evidence regarding quality, safety, and efficacy of

Chart 2. Medicines and their respective therapeutic indications cited in the lawsuits analyzed by the National Cancer Institute José Alencar Gomes da Silva, and present in the Clinical Protocols and Therapeutic Guidelines for Oncology and whose incorporation has been recommended by the Brazilian National Committee for Health Technology Incorporation.

Medicines included in the Clinical Protocols and Therapeutic Guidelines	
Imatinib	<i>Chronic Myeloid Leukemia</i>
Rituximab	<i>Non-Hodgkin's Follicular Lymphoma Diffuse Large B-cell Lymphoma B</i>
Medicines included in the Diagnostic and Therapeutic Guidelines	
Anastrozol	<i>Breast</i>
Bevacizumab	<i>Colon Rectal Colorectal Brain</i>
Bortezomib	<i>Multiple Myeloma</i>
Capecitabin	<i>Breast</i>
Cetuximab	<i>Rectal Colon Colorectal</i>
Cisplatin	<i>Lung</i>
Erlotinib	<i>Lung</i>
Everolimus	<i>Breast Kidney</i>
Exemestane	<i>Breast</i>
Fotemustina	<i>Malignant Melanoma</i>
Gefitinib	<i>Lung</i>
Imatinib	<i>Gastrointestinal Stromal Tumor</i>
Lapatinib	<i>Breast</i>
Oxaliplatin	<i>Metastatic colon</i>
Paclitaxel	<i>Breast</i>
Panitumumab	<i>Metastatic colon Metastatic Rectum</i>
Pazopanib	<i>Kidney</i>
Pemetrexed	<i>Lung</i>
Sorafenib	<i>Liver</i>
Tamoxifen	<i>Breast</i>
Temozolamid	<i>Brain</i>
Temsirolimus	<i>Kidney</i>
Trastuzumab	<i>Breast</i>
Medicines whose incorporation in the SUS has been recommended by the Brazilian National Committee for Health Technology Incorporation (Conitec)	
Rituximab	<i>Non-Hodgkin Follicular Lymphoma Diffuse Large B-cell Lymphoma</i>
Erlotinib	<i>Lung</i>
Trastuzumab	<i>Breast</i>
Imatinib	<i>Gastrointestinal Stromal Tumor Chronic Myeloid Leukemia</i>

such product. On the other hand, the proposal is flexible regarding a possible acquisition, by the government, of a non-registered drug that is not produced in Brazil.

The off-label use of medicines also represents a great risk to the health of the population, considering that the lack of indications is related to insufficient information regarding efficacy and safety²⁷. Although the off-label indications reported in the present study accounted for 16.7% of the indications, it is important to stress that this percentage may be underestimated, because indications presented in the medicine information leaflet are far more specific than those reported in the petitions.

In addition to the increasing rate of therapeutic innovations and the associated high costs, the occurrence of a great variety of tumoural and clinical situations is common among patients with cancer. This reality, as well as the availability of multiple therapeutic choices for a specific cancer case, makes it difficult to define oncological protocols²⁸. Under this perspective, the great majority of procedures follow the DDT rather than the PCDT. An important point is the variability of therapeutic alternatives described in the DDT. Thus, the goals of clinical guidelines are not properly achieved and this favors iniquity in the health system, because the choice of pharmacotherapy remains discretionary.

As a type of logical technology that aims to organize and to standardize the therapeutic conduct based on the best possible evidence²⁹, the level of divergence regarding established oncological protocols and guidelines observed in the lawsuits reveals aspects related to the efficacy of such instruments for guiding prescribing physicians. This applies also to the choices of the judiciary regarding the adoption of a rationale based on rights to health, in decisions opposing the protocols so as to meet individual peculiarities, or the indication of ineffectiveness of treatments provided by the public health system.

Dias and Silva Junior⁶ analyzed the decisions made by Brazilian courts regarding the adoption of the evidence-based medicine rationale and questioned if the judiciary has taken into account the existing clinical protocols when deciding for the supply of a medicine or a service. These authors observed that the presentation of the best available evidence has not been important for the judgement. What prevails are the legal arguments related to health rights, or to the abuse of contractual terms, based on the Consumer Protection Code, or to the lack of demonstration of

the experimental nature of the treatment. They exemplify that, in a certain case, the judge had suggested that the patient's physician, and not the health insurance plan or the State, should decide about the treatment or the medicine to be provided. Such situations illustrate the complexity of the topic "judicialization of health" and the importance of studies on this subject to enable a better comprehension about its dynamics.

Despite the incorporation of new technologies, 12 out of 20 deliberations on cancer drugs requests have been favorable to the Conitec between July 2012 and July 2015⁷. The incorporation process depends on the government capacity to pay for supplies and services, in addition to the analyses of evidence and cost-effectiveness carried out by the Conitec. In the present study, four of the medicines in the lawsuits had been indicated for incorporation into the SUS, presuming a centralized purchase by the federal government. This strategy of centralization has the objectives of reducing costs for the system, promoting rationing in prescription and use, and minimizing problems with procedure coding. However, it does not represent a standardized list of oncological medicines for the SUS⁷. Under this perspective, the lack of an inclusive list of antineoplastic medicines and the high cost of oncological drugs are challenges that need to be overcome in order to guarantee the integrity of care. Problems to access cancer treatment have been reported and result in delays in therapy initiation and in defined health consequences³⁰⁻³².

Observing the data set, it seems to be a mismatch among the available instruments for the analysis of lawsuits. There are SUS-incorporated medicines that should have a protocol of use; however, they have been described as DDT (e.g., erlotinib). In addition, off-label indications are described in the DDT (e.g., cisplatin). Moreover, some medicines that are in the WHO list of essential medicines were not even included in the PCDT (e.g., fludarabine). These inconsistencies compromise the integrity of care and may lead to lawsuits.

In addition to the issues previously pointed out, another aspect deserves attention: the financial amounts involved in the analyzed lawsuits. The amounts related to requests for antineoplastic drugs cited in the literature are significant² and seem to be in line with those reported in the present study. The total estimated amount of over R\$ 18 million for the 158 judicial processes in this analysis, for which the mean amount per process was R\$ 222,582.88, reinforces the impor-

tance of organizing the access to these expensive medicines within the health system.

The novel medicines for cancer treatment have been considered the main reason for the increasing costs of oncological therapies³³. The high prices of newly released oncological medicines and the cost/clinical benefits ratios claimed by the patent holders have been a subject of discussion³⁴. The 10 most expensive medicines identified in the present study are an example of the influence that market prices had on the costs of the evaluated requests and indicate the urgent need for the adoption of strategies to reduce purchase costs and for the use of economic analyses to assist the process of decision-making regarding the incorporation of antineoplastic drugs³⁵.

It should be highlighted that there is no budget allocation to cover lawsuits, which compromises financial resources that could be used in other planned health actions and services or for the purchase of other medicines considered essential for the population. Strategies for contingencies in the judicialization process should be adopted to ensure individual social rights without impairing collective rights, such as the following: to use the principle of health jurisdiction, to comply strictly with the SUS regulations, to develop strategies of joint liability, to favor collective actions, to use technical support groups for decision-making, to update the list of essential medicines and the SUS protocols, to implement a sustainable policy for incorporation of medicines, and to create civil courts specialized for the field of health^{36,37}.

Some limitations of the present study should be mentioned. First, the results obtained derived from judicial processes that were spontaneously referred to the INCa by federal entities; these do not represent all the lawsuits for the provision of antineoplastic medicines in the country. Another point is the fact that the accesses to the websites of Anvisa, Conitec and WHO were subjected to their information updating, made by each entity. In addition, information about the estimated monetary amounts of lawsuits does not correspond to the governmental expenses of the federal entities.

However, the analysis of the lawsuits referred to the INCa during the selected period allowed the identification of some relevant aspects of the pharmaceutical services in oncology in the country. The analysis of the iceberg tip disclosed a dichotomized reality: the urgent need to ensure an efficient and safe use of expensive pharmaceutical technologies for oncological care, in this case

through the PCDT-Onco, and the lack of institutional mechanisms to organize the provision of these treatments by the SUS.

The decreased proportions of antineoplastic drugs and therapeutic indications available in the list of essential medicines of the WHO and in current clinical protocols and guidelines

in Brazil, for which only some particular cases have established funding instruments, indicate the importance of broadening the debate about alternative models that can ensure an effective integral therapeutic assistance to patients under cancer treatment within the Brazilian public health system.

Collaborations

TJ Vidal, EL Moraes, MPF Retto and MJS Silva participated in all stages of the study, from designing the study, analyzing data, writing the article to approving the final version.

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Article submitted 25/10/2016

Approved 10/04/2017

Final version submitted 12/04/2017