Pharmaceutical Assistance to Oncological Patients Using Monoclonal Antibodies in a Reference Hospital in the West of Santa Catarina

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Assistência Farmacêutica a Pacientes Oncológicos em Uso de Anticorpos Monoclonais em um Hospital de Referência do Oeste de Santa Catarina

Asistencia Farmacéutica a Pacientes Oncológicos que Utilizan Anticuerpos Monoclonales en un Hospital de Referencia en el Oeste de Santa Catarina

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ABSTRACT

Introduction: The use of monoclonal antibodies has been incorporated into cancer treatment protocols, once their effectiveness has been proven. This type of therapy is costly and its acquisition is still an obstacle for the patient. **Objective:** To describe the use of monoclonal antibodies in the perspective of purchasing, regulation and judicialization, adverse effects and causes of therapy discontinuation. **Method:** Descriptive study evaluating patients (n=169) undergoing treatment for cancer in a public hospital, from August 1, 2017 to July 31, 2019. **Results:** The population investigated consisted mostly of females (n=115). The main neoplasms found were breast (n=64, 36.16%), lymphomas (n=53, 29.94%) and plasma cell/plasmacytoma multiple myeloma (n=25, 14.12%). The most used monoclonal antibodies were trastuzumab (n=65, 35.71%) and rituximab (n=54, 29.67%). Four forms of drug purchase were observed. The purchases through the National Health System (SUS) (n=103, 56.59%) and law-mandated (n=72, 39.56%) prevailed. Most patients had no therapy-related adverse effects (60.3%), but among those who did, the main effects were vomiting and nausea, asthenia, diarrhea, pain, neutropenia and mucositis. Adverse effects/toxicity (n=15), lack of medication (n=11) and delayed approval (n=10) were the most common causes of treatment discontinuation. **Conclusion:** Monoclonal antibodies are more specific and have lesser effects. For drugs unavailable at SUS, judicialization is an important tool.

Key words: pharmaceutical services; antibodies, monoclonal/therapeutic use; antibodies, monoclonal/adverse effects; neoplasms/drug therapy; health's judicialization.

RESUMO

Introdução: A utilização dos anticorpos monoclonais vem sendo incorporada aos protocolos de tratamento para câncer, uma vez comprovada sua eficácia. Essa modalidade de terapia é onerosa, e sua aquisição ainda constitui um obstáculo para o paciente. **Objetivo:** Descrever a utilização de anticorpos monoclonais no que tange à forma de aquisição, regulação e judicialização, efeitos adversos e causas de interrupção da terapia. **Método:** Estudo descritivo com avaliação de pacientes (n=169) em tratamento para câncer, em um hospital público, no período de 1 de agosto de 2017 a 31 de julho de 2019. **Resultados:** A população estudada foi majoritariamente feminina (n=115). As principais neoplasias encontradas foram de mama (n=64, 36,16%), linfomas (n=53, 29,94%) e mieloma múltiplo de plasmócito/plasmocitoma (n=25, 14,12%). Os anticorpos monoclonais mais utilizados foram o trastuzumabe (n=65, 35,71%) e rituximabe (n=54, 29,67%). Foram observadas quatro formas de aquisição dos fármacos. As aquisições por meio do Sistema Único de Saúde (SUS) (n=103, 56,59%) e judicial (n=72, 39,56%) prevaleceram. A maioria dos pacientes não apresentou efeitos adversos à terapia (60,3%); mas, entre os que apresentaram, os principais efeitos foram vômitos e náuseas, astenia, diarreia, dor, neutropenia e mucosite. Efeitos adversos/toxicidade (n=15), falta de medicamento (n=11) e atraso na liberação (n=10) foram as causas mais comuns de interrupção do tratamento. **Conclusão:** Os anticorpos monoclonais são mais específicos e apresentam menores efeitos. Aos fármacos indisponíveis pelo SUS, a judicialização mostra-se como uma ferramenta importante.

Palavras-chave: assistência farmacêutica; anticorpos monoclonais/uso terapêutico; anticorpos monoclonais/efeitos adversos; neoplasias/tratamento farmacológico; judicialização da saúde.

RESUMEN

Introducción: El uso de anticuerpos monoclonales se ha incorporado a los protocolos de tratamiento del cáncer, una vez comprobada su eficacia. Este tipo de terapia es costosa y su adquisición sigue siendo un obstáculo para el paciente. **Objetivo:** Describir el uso de anticuerpos monoclonales en términos de adquisición, regulación y judicialización, efectos adversos y causas de interrupción de la terapia. **Método:** Estudio descriptivo que evaluó a pacientes (n=169) en tratamiento por cáncer, en un hospital público, desde el 1 de agosto de 2017 al 31 de julio de 2019. **Resultados:** La población estudiada fue mayoritariamente femenina (n=115). Las principales neoplasias encontradas fueron mama (n=64, 36,16%), linfomas (n=53, 29,94%) y mieloma múltiple de células plasmáticas/plasmocitomas (n=25, 14,16%). Los anticuerpos monoclonales más utilizados fueron trastuzumab (n=65, 35,71%) y rituximab (n=54, 29,67%). Se observaron cuatro formas de adquisición de fármacos. Predominaron las adquisiciones a través del Sistema Único de Salud (SUS) (n=103, 56,59%) y judiciales (n=72, 39,56%). La mayoría de los pacientes no presentaron efectos adversos a la terapia (60,3%), pero entre los que sí los tuvieron, los principales efectos fueron vómitos y náuseas, astenia, diarrea, dolor, neutropenia y mucositis. Los efectos adversos/toxicidad (n=15), la falta de medicación (n=11) y la liberación retardada (n=10) fueron las causas más frecuentes de interrupción del tratamiento. **Conclusión:** Los anticuerpos monoclonales son más específicos y tienen menos efectos. Para los medicamentos no disponibles en el SUS, la judicialización es una herramienta importante.

Palabras clave: servicios farmacéuticos; anticuerpos monoclonales/uso terapéutico; anticuerpos monoclonales/efectos adversos; neoplasias/tratamiento farmacológico; judicialización de la salud.

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INTRODUCTION

Monoclonal antibodies are biopharmaceutical compounds which have gained relevance in the list of available therapies to fight cancer and impacted the pharmaceutical industry, although their creation is not recent. According to their biological structure, there are four different ways to characterize the antibodies: murine (or full mouse proteins), chimeric, humanized and fully human proteins[1-3].

Targeted-therapy and immunotherapy utilize monoclonal antibodies, the first consists in antibodies which bind to specific antigens of the tumor to attack them. The mechanisms to attack the tumor are similar to those for micro-organisms as opsonization, phagocytosis, complement activation system and antibodies-dependent cellular cytotoxicity. Immunotherapy strengthens the patient's immune system to fight more effectively the pathogenic cells[1,2].

Monoclonal antibodies utilized as antineoplastics in Brazil are: nivolumab, ipilimumab, brentuximab vedotin, bevacizumab, ramucirumab, cetuximab, nimotuzumab, panitumumab, rituximab, obinutuzumab, ofatumumab, pertuzumab, trastuzumab and trastuzumab emtansine. The main tumors treated by these medications are colorectal, lung, breast, renal cells, ovary, uterine tube, peritoneal, cervix, gastric, head and neck and melanoma[4]. The side effects documented mostly are fever, chills, asthenia, headache, nausea, vomit, diarrhea, arterial hypotension, rash and hypersensitivity[1,5-8]. Even with these side effects, patients' survivorship with cancer is, overall, greater with these medications comparing with those who do not use them, including monotherapy[9].

Due to the relevance of the theme, the poor characterization in other studies and the great impact on the morbimortality of the patients, this study had the objective of describing the utilization of monoclonal antibodies according to the form of acquisition, adverse effects and motives to discontinue the therapy, in addition to the sociodemographic characterization and main neoplasms encountered in patients consulted by "*Hospital Regional do Oeste*" in Santa Catarina from August 2017 to July 2019.

METHOD

Descriptive study with data collected at the hospital's oncology and pharmacy from August 1, 2017 to July 31 at "*Associação Lenoir Vargas Ferreira*" of "*Hospital Regional do Oeste*" in Chapecó, Santa Catarina. Online charts were collected at the hospital's facilities at a previously agreed schedule with the team with login and access to the investigators provided by the institution. The following data were obtained from the charts: name, age, sex and occupation to characterize the sample, classification according to the International Classification of Diseases and Related Health Problems – 10th edition (ICD-10)[10], year of diagnosis, chemotherapy protocols utilized, adjuvant or neoadjuvant therapy and monoclonal antibodies utilized. The form of acquisition was investigated to analyze the antibodies individually: National Health System (SUS), Complementary, Legal and other including antibodies sharing among patients, further to complications of the therapy, of parenteral administration and motive to discontinue the treatment.

The inclusion criteria were patients admitted, in outpatient treatment and deceased with solid and/or hematological neoplasms in oncologic treatment with monoclonal antibodies.

Size sample was given by the formula:

$$n = [EDFF*Np(1-p)]/[(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$$

Where: *n* is the size of the sample, EDFF is the effect of the design (1), N is the size of the population (302), p is the hypothetical frequency of the factor of the result on the population (27%), d is the confidence level (5%), and *Z* is the deviation of the mean value accepted to reach the intended confidence level. The software Epi Info™ version 7.2.3.1 was utilized for the calculation.

The percent of adverse effects utilized for the hypothetical frequency of the sample size was obtained from the study *Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients*[11] because trastuzumab is the most prevalent antibody, in addition to the difficulty in finding similar studies and therapy adverse effects, one of the main themes addressed in the study. In this case, there was an incidence of 27% of side effects utilized for the calculation.

For representativeness of ten monoclonal antibodies of the sample, this percentage was utilized to determine the number of patients of each antibody. The patients were grouped per medication, in alphabetic order, numbered in ascending order and each group beginning in 1. Later, the participants were randomly assigned to be included in the study with the tool available electronically at the website of Epi Info™ version 7.2.3.1; at the corresponding fields, the first and last number of each one of the groups of antibodies and the random numbers generated were added according to the final n calculated for each group of antibodies.

The Institutional Review Board of "*Universidade Federal da Fronteira Sul*" approved the study, report number 3,997,777 on April 29, 2020 (CAAE: 30082220.0.0000.5564).

RESULTS

In the period investigated, 302 patients were consulted. The minimum significant sample was 152 patients, eventually, 169 charts were evaluated.

Table 1 shows the prevalence of 68.05% of female patients (n=115) over the male population (n=54, 31.95%). The mean age in the two populations is 40-69 years old. For 63.91% of the charts (n=108), the occupation was not informed and the main occupation was farmer (8.9%) followed by retired (7.7%).

The neoplasms encountered were grouped in 22 types (n=177) and respective ICD. Some patients were classified in more than one type or subtype of cancer during the period investigated. Table 2 shows that the most frequent was breast cancer in 64 patients (36.16%) followed by lymphomas in 53 patients (29.94%) and multiple myeloma/plasmacyte malignant neoplasm/plasmacytoma in 25 patients (14.12%).

The most prevalent monoclonal antibody was trastuzumab (35.71%, n= 65) which is utilized to treat breast cancer, followed by rituximab (29.67%) and bortezomib (13.74%). The least found were cetuximab (0.55%), daratumumab (1.1%) and brentuximab (1.65%) as shown in Graph 1A. Of the 169 patients evaluated, 16 (9.5%) used more than one monoclonal antibody. The association of trastuzumab with pertuzumab was the most common (63%) according to Graph 1B.

The objective of using monoclonal antibodies in oncologic therapy is to achieve more effectiveness and

Table 1. Sociodemographics of patients admitted at Hospital Regional do Oeste

Variables			Mean	Standard Deviation
Age-range	**Female n (%)**	**Male n (%)**		
20-29	0	1 (1.9)	0.5	0.7
30-39	15 (13.0)	3 (5.6)	9	8.5
40-49	26 (22.6)	8 (14.8)	17	12.7
50-59	34 (29.6)	10 (18.5)	22	17.0
60-69	30 (26.1)	18 (33.3)	24	8.5
70-79	9 (7.8)	10 (18.5)	9.5	0.7
80 or more	1 (0.9)	4 (7.4)	2.5	2.1
Total	115 (100)	54		
Occupation	**n**	**%**		
Not informed	108	63.91		
Farmer	15	8.88		
Retired	13	7.69		
Kitchen server	1	0.59		
Production aide	2	1.18		
Carpenter	1	0.59		
Trader	3	1.78		
Confectioner	2	1.18		
Seamstress	2	1.18		
Cooker	2	1.18		
Housewife	7	4.14		
Housekeeper	1	0.59		
Esthetician/hairdresser/manicure	2	1.18		
Instructor	1	0.59		
Machine operator	1	0.59		
Bricklayer	1	0.59		
Teacher	4	2.37		
Cleaning assistant	1	0.59		
Garment industry worker	1	0.59		
Small farm worker	1	0.59		
Total	169	100		

Table 2. Types of neoplasms found in oncologic patients at a Santa Catarina West hospital

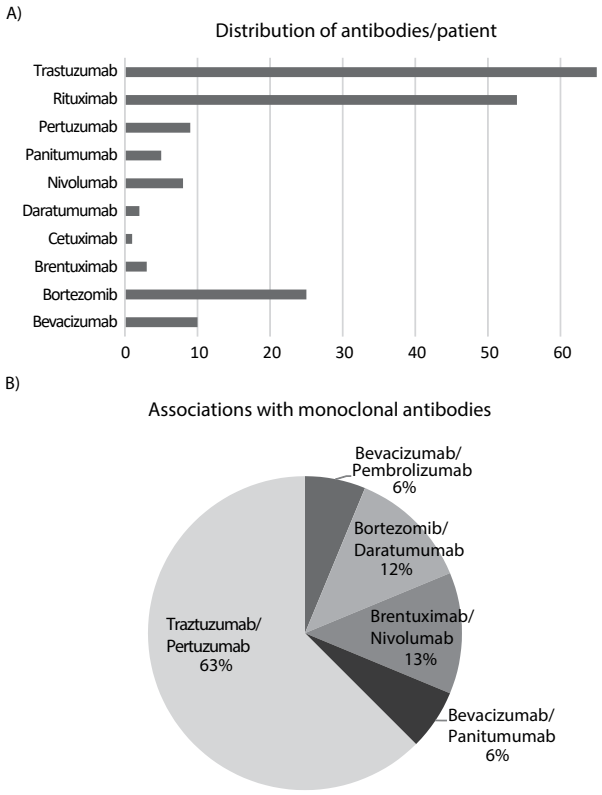
Type of cancer	n	%	ICD
Keratinizing-type squamous cells	1	0.56	C34
Colon	5	2.82	C18, C189
Heart, mediastinum and pleura with invasive lesion	1	0.56	C388
Stomach	1	0.56	C16
Glioblastoma	1	0.56	C71
Liver	2	1.13	C220
Chronic Lymphocytic/lymphoid leukemia	5	2.82	C911
Nodular sclerosis, Hodgkin's lymphoma	4	2.26	C82, C811
Non-Hodgkin's Lymphoma	49	27.68	C82, C822, C833, C857, C911, C838
Breast	64	36.16	C50, C504, C508, C509
Nipple and areola	1	0.56	C500
Melanoma	2	1.13	C43
Multiple myeloma and malignant plasmacyte neoplasm	23	12.99	C90, C900
Neoplasm of appendix	1	0.56	C18
Skin of the lip	1	0.56	C440
Plasmacytoma of column	2	1.13	C900
Pleura	1	0.56	C384
Lung	1	0.56	C340
Sigmoid/upper/lower /rectosigmoid rectum	8	4.52	C20, C189, C19, C188, C187
Kidney, except renal pelvis	1	0.56	C64
Connective tissue and soft tissues of abdomen and thorax	2	1.13	C494
Uterus	1	0.56	C54
Total	177	0.56	

Caption: ICD = International Classification of Diseases and Related Health Problems – 10th Edition.

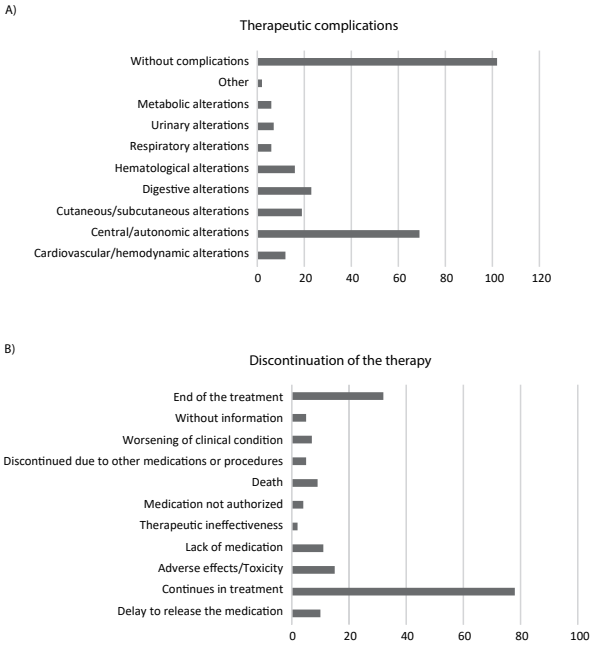
less adverse effects because of the selectiveness of the antibody to the target antigen. Graph 2A shows that 102 patients (60.3%) had no complications during therapy, the most prevalent for those who had were autonomic/central alterations (26.3%) followed by digestive (8.8%), cutaneous/subcutaneous (7.3%), hematologic (6.1%), cardiovascular/hemodynamic (4.6%), urinary (2.7%), respiratory and metabolic (2.3% each) and other (0.8%). The main symptoms were vomits and nausea (n=20), asthenia (n=15), diarrhea (n=12), pain (n=12), neutropenia (n=10) and mucositis (n=8). Graph 2B demonstrates that 32 patients (19%) discontinued the treatment and some, more than once for different reasons. The main causes of discontinuation were adverse effects and toxicity (n=15), lack of medications (n=11) and delay to release the drugs (n=10). In addition, 72 patients continued in therapy at the end of the study.

Graph 3A shows that the main form of acquisition of medications was through SUS with 103 antibodies, 56.59% among the 182 antibodies evaluated. The second most prevalent was by legal means with 72 monoclonal antibodies (39.56%), and third and fourth, SUS/legal and legal/other, respectively. These mixed forms were found in 3.85% of the antibodies, being 2.75% through SUS and legal for trastuzumab, and 1.1%, mixed, legal and other for bortezomib.

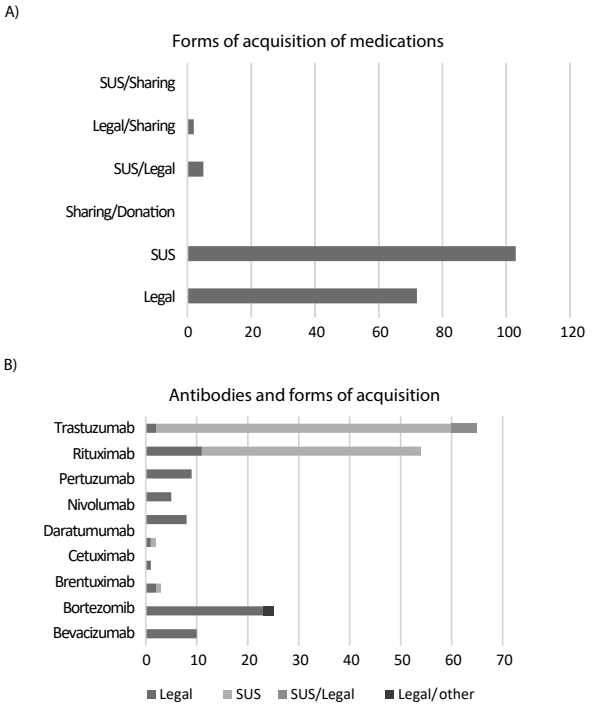
Graph 3B shows that the main monoclonal antibodies encountered were trastuzumab (n= 65) and rituximab (n= 54), both distributed mainly by SUS. The monoclonal antibodies cetuximab, nivolumab, panitumumab, pertuzumab, bevacizumab were fully obtained by judicialization, bortezomib, 92%, daratumumab, 50% and brentuximab, 66.67%. The lowest rates were trastuzumab (3.08%) and rituximab (20.37%). The total percentage of medications obtained by judicialization was 39.56%.



Graph 1. Monoclonal antibodies and associations administered to oncology patients at a hospital of the West region of Santa Catarina. (A) Distribution of monoclonal antibodies to oncology patients who used this therapy (n=182); (B) Associations of the use of monoclonal antibodies



Graph 2. Therapeutic complications and interruption of the therapy in patients in use of monoclonal antibodies at a hospital of the West region of Santa Catarina. (A) Complications during the treatment with monoclonal antibodies (n=262); (B) Factors related to the interruption of the therapy with monoclonal antibodies (n=100)



Graph 3. Monoclonal antibodies and acquisition. (A) Form of acquisition of the medications (n=182); (B) Antibodies and forms of acquisition (n=182)

DISCUSSION

The estimates of the National Cancer Institute José Alencar Gomes da Silva (INCA) show that for each year of the triennium 2020-2022, the most incident neoplasms, except skin, are prostate, colon and rectum in men and breast, colon and rectum in women. Lymphomas are incident for both and are one of the ten most prevalent types[12]. In the current study, the most frequent cancers were breast cancer (n=64, 36%), lymphomas (n= 53, 30%) and multiple myeloma/neoplasm of plasmacyte/ plasmacytoma (n=25, 14%), reaching 80%. The prevalence of these types of cancer reflects the main antibodies administered to the patients as trastuzumab (35,7%), rituximab (30%) and bortezomib (114%). Some antibodies, despite the prescription for certain oncological diseases, are not offered by SUS as, for instance, trastuzumab for advanced gastric cancer and rituximab for chronic lymphoid leukemia[13-15].

The most common association of monoclonal antibodies is trastuzumab and pertuzumab found in ten patients although the report of the 53rd meeting of the National Commission of Incorporation of New Technologies by SUS (Conitec) has initially rejected this association and docetaxel to treat metastatic HER-2 positive breast cancer as first line of treatment. The justification was that most of the patients of the main study submitted were

trastuzumab-treatment-naive, the profile of the patients enrolled in the study is different than non-study patients, the incorporation of pertuzumab was not cost-effective and had significant impact on the health system[16].

For all the antibodies investigated, at least one adverse reaction was reported. Most of the effects encountered were related to trastuzumab, rituximab, bevacizumab and bortezomib. Abdominal pain, tiredness, chest pain, chills, fever, headache, diarrhea, nausea, vomit, joint pain, muscle pain and skin marks can occur with trastuzumab. Severer signs may be noticed additionally as reduced left ventricular ejection fraction leading to heart failure, a symptom described in up to 22% of the patients[13].

Rituximab can increase susceptibility to infections of the upper respiratory tract, urinary tract infections, neutropenia, hypertension, nausea, rash, pyrexia, pruritus, hives, sore throat, blush with local heat, hypotension, rhinitis, tremors, tachycardia, fatigue, oropharynx pain, peripheral edema, erythema, hypercholesterolemia, paresthesia, migraines, dizziness, headache, alopecia, dyspepsia, diarrhea, gastroesophageal reflux, oral ulcer, abdominal pain, arthralgia/musculoskeletal pain, osteoarthritis and bursitis[14,17]. Bortezomib can cause neuropathy, arterial hypotension, cardiac failure, alterations of the liver function, thrombocytopenia, neutropenia, gastrointestinal and intracerebral bleeding, nausea, diarrhea, constipation, vomits, vertigo, dizziness or fainting[15].

Vaz et al.[18] concluded in a study with trastuzumab alone more prevalence of tiredness as adverse effect (45%), followed by xeroderma (27%), leg pain (18%) and vomit (9%). When associated with chemotherapy, the main symptoms were tiredness (26%), body pain (26%), leg pain (13%), nausea (13%), shortness of breath (13%) and vomit (6.7%)[18].

During therapy, 102 patients (603%) did not report any adverse effect, the most reported for the patients who did were nausea and vomits, asthenia, diarrhea, pain, neutropenia and mucositis. While evaluating adverse effects, however, other concomitant chemotherapy medications/therapy were utilized by the patients or clinical conditions-related symptoms.

Public policies targeted to oncologic attention have ensured the patients extended global survivorship with better quality-of-life. Part of this success should be credited to the progress of drug therapy[9]. An issue not to be overlooked to increase survivorship and effectiveness of the treatment is the legal support to use more effective drugs as monoclonal antibodies[4,19]. It is quite clear the dependence relation of legal lawsuits and implementation of technologies by SUS through Conitec. Without the actual knowledge of the population demands for a medication, quite often expensive, it is unfeasible the implementation of public policies to incorporate them into the available cost-free inventory offered by SUS[20].

The elevated cost is one of the major problems to prescribe these medications, reason for which several monoclonal antibodies are not available at the National List of Essential Medications (Rename)[21] and consequently at SUS. Lawsuits are a possibility, even if costly, to solve this question. In ten years, there was nearly a 5 thousand per cent increase of legal costs in Brazil, ranging from R$ 26 million to more than R$ 1,325 billion between 2007 and 2016[22]. The number of health-related first instance processes accelerated from 2009 to 2017, a growth of 198%. In 2017, 95.7 thousand lawsuits started to be processed by the Brazilian judiciary[23]. In some States, antineoplastics are the medications most pledged judicially[24-26], and monoclonal antibodies are second in demand as concluded by a study in the State of Pernambuco[27]. As some monoclonal antibodies are not addressed by Conitec[21], lawsuits for this class of medications are high, some of them are obtained fully with legal support.

The present study showed that 39.56% of monoclonal antibodies investigated were obtained by legal means. The rising number of lawsuits is for medications non-standardized by Conitec or with reimbursable value incompatible with the medication cost.

The different forms of acquisition of medications investigated were in descending order: SUS; legal; SUS/legal and legal/other. For the first, trastuzumab and rituximab are the main drugs, already offered by SUS with proven efficacy for certain treatments only in the last ten years and approved by Conitec after extensive systematic reviews and meta-analyzes and positive survivorship results. Trastuzumab is prescribed by SUS only for neoadjuvant, adjuvant and metastatic HER2+ breast cancer, except bone cancer. Rituximab is prescribed only for large cell diffuse non-Hodgkin's lymphoma and follicular lymphoma as first and second line. The current study concluded that 56.59% of monoclonal antibodies prescribed at the most are acquired administratively by SUS. The study by Schulz et al.[17] revealed that rituximab-induction treatment associated with chemotherapy achieved better results of global survival (hazard ratio – HR = 0.63; confidence interval of 95% – CI 95% = 0.51-0.79)[17].

The medications requiring law enforcement actions were cetuximab, nivolumab, panitumumab, pertuzumab, bortezomib, bevacizumab and brentuximab, which, although approved by Conitec to be offered by SUS were not obtained by this mean. The judicialization may occur because some of them may be missing, recent inclusion as bortezomib approved in 2020 or use for other cancers

than those approved originally. A class action in the State of Santa Catarina number 5019190-76.2019.4.04.7200 determined the offer of trastuzumab for patients with HER2+ bone and visceral metastases. The supply is not continuous and many women utilized the legal system to avoid loss of follow-up. Due to the inconsistency of the medical prescription with the protocol, only trastuzumab was acquired by SUS/other. Bortezomib, the only monoclonal antibody acquired by judicialization/other is a form the doctor prescribed utilizing stable pharmacological leftovers from patients who used smaller doses than the vial's until the legal approval is obtained and continuous offer.

Public policies that encourage the medical, scientific, social and legal community to submit Conitec revisions with clinical evidences to approve the offer of this medication by SUS, most of all of therapies already approved internationally with curative potential or good therapeutic or palliative response for fatal and incapacitating diseases as several types of cancer are important.

The major difficulty found is the flawed completion of some charts with excess of abbreviations, missing and disorganized data which is an obstacle to understand the information.

CONCLUSION

Breast cancer and hematological neoplasms – lymphomas and myeloma – were the predominant neoplasms submitted to monoclonal antibodies therapy in the present study. Women between 40 and 59 years of age are the most prevalent, reinforcing the necessity of early diagnosis and continuous therapeutic monitoring which can be negatively affected by the overload of the health system.

The choice of monoclonal antibodies therapies minimizes the adverse effects but still quite evident. The effects described in the literature were similar to those found in the current study. These therapies are combined with others, including chemotherapics.

Acquisition of monoclonal antibodies by SUS is prevalent notwithstanding the significant impact of law-mandated purchasing. The population utilizes the law to obtain monoclonal antibodies if not offered by SUS and be treated by the Federal Government, States or municipalities, which highlights the importance of public policies in place encouraging the medical, social and legal community to submit to Conited revisions with clinical evidences to approve the incorporation of new technologies to ensure the backbone principles of the health system as equity, integrality and universality.

Unfortunately, therapy can be discontinued due to toxicity, lack of medication and delay to approve the antibodies.

The data obtained point out the necessity of continuous updating based in scientific articles, reduction of side effects, increase of life expectancy, inclusion in the list of high complexity medications, decision by the managing team, legal actions and mainly, benefits to the patients who need this therapy.

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CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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None.

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