Immunotherapy in Oncology in a Countryside City of Minas Gerais: Analysis of the decade 2010-2019

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Imunoterapia em Oncologia em uma Cidade do Interior de Minas Gerais: Análise da Década 2010-2019

Inmunoterapia en Oncología en una Ciudad del Interior de Minas Gerais: Analisis de la Década 2010-2019

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ABSTRACT

Introduction: In recent years, systemic therapy in oncology has undergone substantial changes and immunotherapy has spread out as a form of adjuvant treatment. In Brazil, differences of access to this therapy are relevant and there is still no extensive knowledge about the use of immunotherapy in different regions of the country. **Objective:** To analyze the panorama of immunotherapy in cancer treatment in Barbacena-MG in the last decade. **Method:** Single-centre descriptive study. Patients over 18 years diagnosed with cancer who used immunotherapies in the period from 2010 to 2019 were selected by reviewing the Hospital Cancer Registry and the information contained in this system, as well as charts, were used to obtain sociodemographic and clinical data. **Results:** Immunotherapy was used to treat 90 patients (4.9%), totalling 95 treatments. Bacillus Calmette-Guérin (BCG), trastuzumab and imatinib were the drugs most used. There was an increase in the use of immunotherapeutic agents over the decade, as well as in the variety of treatments performed. Imatinib and pazopanib had a higher percentage of deaths during treatment and 77.9% of the drugs used were funded by the Unified Health System (SUS). Treatment duration for most patients remained close to 10 months, being shorter for those who were treated with BCG. **Conclusion:** The use of immunotherapy in oncology in Barbacena has grown from 2010 to 2019, in number and variety of treatments, with incorporation of new drugs.

Key words: Neoplasms/therapy; Immunotherapy; Brazil.

RESUMO

Introdução: Nos últimos anos, a terapia sistêmica em oncologia sofreu mudanças substanciais e a imunoterapia destacou-se como forma de tratamento adjuvante. No Brasil, as diferenças do acesso a essa terapêutica podem ser observadas de maneira relevante e ainda não há amplo conhecimento sobre o seu uso nas diferentes Regiões do país. **Objetivo:** Analisar o panorama da utilização de imunoterapia no tratamento oncológico em Barbacena-MG na última década. **Método:** Estudo descritivo de centro único. Os pacientes maiores de 18 anos, diagnosticados com câncer e que utilizaram imunoterápicos no período de 2010 a 2019, foram selecionados por meio de consulta ao Registro Hospitalar de Câncer, e as informações constantes nesse sistema, bem como prontuários, foram utilizadas para obtenção de dados sociodemográficos e clínicos. **Resultados:** A imunoterapia foi utilizada no tratamento de 90 pacientes (4,9%), totalizando 95 tratamentos. Entre os medicamentos utilizados, destacaram-se o Bacillus Calmette-Guérin (BCG), o trastuzumabe e o imatinibe. Observou-se um aumento na utilização de imunoterápicos ao longo da década, bem como uma maior variedade de tratamentos realizados. O imatinibe e o pazopanibe obtiveram maior porcentagem de óbitos durante o tratamento e 77,9% dos medicamentos utilizados foram custeados pelo Sistema Único de Saúde (SUS). O tempo de tratamento da maioria dos pacientes se manteve próximo a dez meses, sendo menor para aqueles que se trataram com BCG. **Conclusão:** O uso da imunoterapia em oncologia em Barbacena apresentou um avanço no período de 2010 a 2019, tanto no quantitativo quanto na variedade de tratamentos, com incorporação de novos medicamentos.

Palavras-chave: Neoplasias/terapia; Imunoterapia; Brasil.

RESUMEN

Introducción: En las últimas décadas han permitido el desarrollo de nuevas modalidades de tratamientos anticancerosos y la inmunoterapia se ha destacado. En Brasil, el acceso desigual a inmunoterapia es relevante y todavía no hay amplio conocimiento sobre su uso en las distintas regiones del país. **Objetivo:** Analizar el panorama de la inmunoterapia en el tratamiento anticanceroso en Barbacena-MG en la última década. **Método:** Estudio descriptivo de centro único, con datos del Registro Hospitalario de Cáncer y registros médicos de los pacientes que usaron inmunoterapéuticos en el tratamiento anticanceroso de 2010 a 2019. **Resultados:** Se utilizó inmunoterapéuticos para tratar a 90 pacientes (4,9%), totalizando 95 tratamientos. Entre los medicamentos utilizados, se destacaron Bacillus Calmette-Guérin (BCG), trastuzumab e imatinib. Hubo un aumento en el uso de inmunoterapéuticos en la década, así como una mayor variedad de tratamientos realizados. Imatinib y pazopanib tuvieron un mayor porcentaje de muertes durante el tratamiento y 77,9% de los medicamentos utilizados fueron financiados por el Sistema Único de Salud (SUS). El tiempo de tratamiento para la mayoría de los pacientes fue diez meses, siendo más corto para el tratamiento con BCG. **Conclusión:** El uso de la inmunoterapia en oncología en Barbacena ha avanzado en el período de 2010 a 2019, tanto en cantidad como variedad de tratamientos, con incorporación de nuevos medicamentos.

Palabras clave: Neoplasias/terapia; Inmunoterapia; Brasil.

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INTRODUCTION

Cancer is a chronic disease of great prevalence and high morbimortality being currently responsible for one in each six deaths in the world. More than 14 million people develop this disease every year and the estimate is that this figure should escalate to more than 21 million in 2030[1]. For Brazil, it is estimated the occurrence of 625 thousand new cases of neoplasms for each year of the triennium 2020-2022 according to the National Cancer Institute José Alencar Gomes da Silva (INCA)[2].

For decades, the conventional treatment for cancer was the combination of surgery, chemotherapy and/or radiotherapy[3]. However, in the last years, systemic therapy in oncology underwent substantial changes. The advances in understanding genetic abnormalities led to the development of different target-therapies. Some new chemotherapic treatments were approved and other, already well known, have been widely utilized. In addition, better understanding about the interaction of tumor cells and the immune system supported the development of immunotherapies[4].

Immunotherapy promotes the stimulation of the immune system through the use of biological response modifiers. The idea was originally proposed by William Coley in 1893. After, Paul Ehrlich, in 1909, suggested that the immune system should play a role in the fight against cancer[5,6].

Immunotherapy in oncology can be classified in active and passive according to the substances utilized and its mechanisms of action. In active immunotherapy, stimulating and restoring agents of the immune function (nonspecific immunotherapy, for example, biological modifiers as Bacillus Calmette-Guérin – BCG and cytokines) and tumor cells vaccines (specific immunotherapy) are applied with the objective of intensifying the resistance to tumor growth. In passive or adoptive immunotherapy, anti-tumor antibodies or exogenous mononuclear cells are administered with the finality of enhancing the immunologic capacity to fight the disease as monoclonal antibodies[3].

The use of immunotherapy provoked deep transformations in cancer treatment all over the world[7]. However, the arrival of immunotherapeutics did not occur in the same manner in every country and it was influenced by several factors, not only clinic and technical-scientific, but also market dictated[8]. More specifically in Brazil, a continental country where socioeconomic inequities impact the access to health technologies, these differences can be noticed among states and among cities of the same state. Furthermore, there is no wide knowledge about the use of this therapy in the different country regions and it is necessary to evaluate its use and expand the disclosure of information. In this context, the goal of the present study was to analyze the outlook of the use of immunotherapy in oncologic treatment in Barbacena-MG in the last decade.

METHOD

Descriptive study whose object are cancer immunotherapies conducted from 2010 to 2019 in the oncology hospital in Barbacena-MG. The municipality is a regional cancer reference comprehending more than 14 municipalities, which translates in care provided to 225,183 inhabitants[9].

The inclusion criteria were oncologic patients older than 18 years diagnosed with cancer in any stage using immunotherapy to treat malignant neoplasms and treated between 2010 and 2019. Patients who used immunotherapeutics only as modulators of immune response and not as part of the antineoplastic treatment and the patients who were in treatment but were diagnosed in another hospital were excluded.

Patients with cancer who used chemotherapics as part of the therapy were selected by searching the electronic Cancer Hospital Registry (RHC). Pursuant to the criteria chosen, the use of any immunotherapeutic as treatment, the patients were selected. After the patients were selected, the RHC and charts data were utilized to obtain the sociodemographic and clinical information and the following data of follow up/prognosis: (I) immunotherapeutic utilized; (II) beginning and end of the treatment; (III) death during treatment (if applicable).

The Institutional Review Board of the Medical College of Barbacena-MG approved the study, number CAAE 06670919.8.0000.8307, report 3.144.278, dated February 13, 2019 and conducted in compliance with Resolution CNS number 466/12[10].

The data obtained through forms and charts were transcribed to an electronic spreadsheet and processed in statistical software Stata version 9.2. Based in this, tables with absolute and relative frequencies were elaborated. For the quantitative variables, measures of central tendency, position and dispersion were calculated.

RESULTS

In the last decade, 90 patients underwent oncologic treatment with immunotherapy in Hospital Ibiapaba. Of these, five relapsed and were retreated, totaling 95 treatments. In this same period, 1,837 patients were treated in the institution, immunotherapy was utilized in 4.9% of the patients treated. The sociodemographic characteristics of the patients are presented in Table 1. There was more

prevalence of immunotherapeutic treatment in patients older than 61 years, Caucasian. Among the medication used, BCG as biological modifier, trastuzumab as monoclonal antibody and imatinib as inhibitor of protein kinase stand out.

In Table 2, the distribution of the main immunotherapeutic treatments according to topography of cancer and histological types are presented. 100% of the patients treated with BCG had gall bladder cancer; of these, 86 (27%) were transitional cells papillary carcinoma. Three different immunotherapeutics were utilized in different types of cancer. Interferon alfa 2-B for renal cancer and melanoma; denosumab, in breast cancer and multiple myeloma and imatinib, in gastrointestinal tumor and chronic myeloid leukemia.

Table 1. Sociodemographic characteristics of patients (n=90) diagnosed with cancer who received the first treatment with immunotherapeutics in the oncologic treatment hospital, Barbacena-MG, 2010-2019

Characteristics	Variables	n	%
Age (years)	29 to 40	6	6.66
	41 to 50	11	12.21
	51 to 60	18	19.98
	61 to 70	29	32.21
	71 to 80	18	19.98
	>81	8	8.88
Gender	Female	41	45.56
	Male	49	54.44
Race	Caucasian	60	66.67
	Black	6	6.67
	Brown	24	26.67
Education	<9 years	33	36.67
	>9 years	25	27.78
	No information	32	35.56
Alcohol use	No	44	48.89
	Yes	14	15.55
	No information	32	35.56
Tobacco history	No	34	37.78
	Yes	31	34.44
	No information	25	27.78
Immunotherapeutics utilized	**BIOLOGICAL MODIFIERS**	**58**	**61.05**
	BCG	51	53.68
	Interferon alfa-2B	7	7.37
	MONOCLONAL ANTIBODIES	**32**	**33.69**
	Trastuzumab	14	14.74
	Brentuximab	3	3.16
	Rituximab	10	10.53
	Bevacizumab	1	1.05
	MONOCLONAL ANTIBODIES		
	Cetuximab	1	1.05
	Denosumab	3	3.16
	INHIBITORS OF PROTEIN KINASE	**5**	**5.27**
	Imatinib	3	3.16
	Pazopanib	2	2.11

The number of cancer immunotherapies conducted in the hospital analyzed at each biennium of the last decade is shown in Figure 1. A raise of the use of immunotherapeutics along the decade was observed as well as the integration of new drugs in the consecutive years, resulting in a larger variety of treatments conducted.

The deaths during the treatment with immunotherapeutics and its cost between 2010 and 2019 are shown in Table 3. Imatinib and pazopanib were the medications with higher percentage of deaths. Of a total of 51 patients in treatment with BCG, only one patient died. In addition, 77.9% of immunotherapeutics utilized were funded by the National Health System (SUS). The drugs bevacizumab, cetuximab and denosumab were fully funded by non-SUS.

The time of treatment of most of the patients who utilized some immunotherapeutic was near ten months, being lower for patients who were treated with BCG (Figure 2). In addition, trastuzumab presented the highest variation in the total time of the treatment.

DISCUSSION

Immunotherapy is recent and is growing, a result of many innovative findings in immunology and cancer therapy in the last century. However, despite the advances, there are still obstacles for this therapeutic, among them, the impossibility of predicting the effectiveness of the treatment, the necessity of additional biomarkers, development of resistance, lack of optimized study designs to determine the efficacy and the high costs of this treatment[7].

It was observed that between 2010 and 2019, 4.9% of the patients with cancer in the region were treated with immunotherapeutics. They are not still first line treatment for neoplasms, but when used as such, they are not used isolated but associated to other drugs. For this to happen, it is necessary the demonstration of the efficacy comparable or better and reduced toxicity in relation to the current first line agents[7]. In addition, there is a gap between the approval of the drugs in other countries and the approval in Brazil, which delays the availability of immunotherapeutics in the country. When approved by the National Health Surveillance Agency (ANVISA), the oncologic intravenous drugs must be funded by health insurers. Prior to their integration in SUS, they need to be reviewed by the ATS (Evaluation of Health Technologies), approved by the National Commission of Incorporation of Technologies (CONITEC) and then listed in the National Registry of Essential Drugs (RENAME). This is the reason

Table 2. Distribution of the main treatments with immunotherapeutics according to the types of cancer and histological types of the patients treated in the oncology hospital, Barbacena-MG, 2010-2019 (n=78)

Immunotherapeutics	Type of cancer n (%)	Histological type	n (%)
BCG	Gall bladder 51 (100.00)	Transitional cells papillary carcinoma	44 (86.27)
		Transitional cell carcinoma	6 (11.76)
		Papillary carcinoma	1 (1.96)
Interferon alfa 2-B	Kidney 6 (85.71)	Clear cells adenocarcinoma	4 (57.14)
		Renal cell carcinoma	2 (28.57)
	Melanoma 1 (14.29)	Malignant melanoma	1 (14.29)
Trastuzumab	Breast 14 (100.00)	Invasive ductal carcinoma	10 (71.43)
		Ductal adenocarcinoma	1 (7.14)
		Lobular carcinoma	1 (7.14)
		Invasive ductal carcinoma	1 (7.14)
		Paget's disease of the breast	1 (7.14)
Denosumab	Breast 2 (66.67)	Invasive ductal carcinoma	2 (66.67)
	Multiple myeloma 1 (33.33)	Plasmocytic myeloma	1 (33.33)
Imatinib	Gastrointestinal stromal tumor 1 (33.33)	Gastrointestinal stromal sarcoma	1 (33.33)
	Chronic myeloid leukemia 2 (66.67)	Chronic granulocytic leukemia (SOE)	2 (66.67)

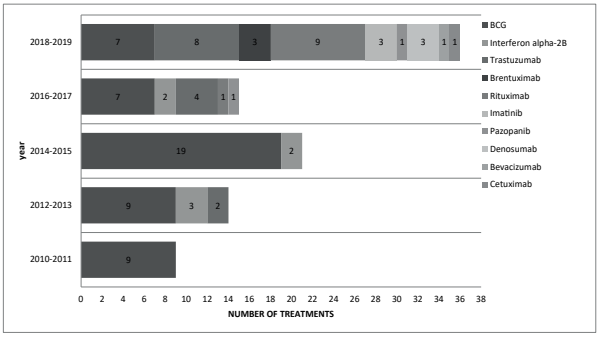

Figure 1. Number of treatments with immunotherapeutics for each biennium of the decade 2010-2019 in the oncologic treatment hospital, Barbacena-MG (n=95)

why there are differences between what is registered and what is utilized in non-public health systems in relation to what SUS provides[7].

Table 3. Deaths (n=90) during the treatment with immunotherapeutics and cost of the treatment of the patients treated in the oncologic hospital, Barbacena-MG, 2010-2019

Immunotherapeutics	Deaths n (%)	SUS	Non-SUS
BCG	1 (1.96)	43 (84.31)	8 (15.69)
Interferon alfa-2B	4 (57.14)	6 (85.71)	1 (14.29)
Trastuzumab	2 (14.29)	11 (78.57)	3 (21.43)
Brentuximab	1 (33.33)	1 (33.33)	2 (66.67)
Rituximab	3 (30.0)	8 (80.00)	2 (20.0)
Bevacizumab	0	0	1 (100.0)
Cetuximab	0	0	1 (100.0)
Denosumab	0	0	3 (100.0)
Imatinib	3 (100.0)	3 (100.0)	0
Pazopanib	2 (100. 0)	2 (100.0)	0
TOTAL	**16 (17.8)**	**74 (77.9)**	**21 (22.1)**

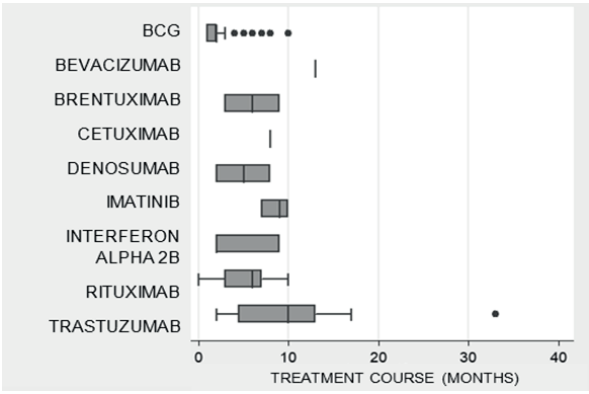

Figure 2. Time of treatment in months for each immunotherapeutic utilized by patients who concluded the treatment in the Oncology Department of Hospital Ibiapaba, Barbacena-MG, 2010-2019 (n=95)

Gall bladder, breast and lymphoma are the cancers most treated with immunotherapeutics in Barbacena-MG during the period investigated, more frequent for patients older than 50 years. This data corroborates the statistics of INCA where these tumors are more prevalent from this age-range[2]. The mean age for diagnosis of gall bladder is 72 years, more than 70% of the patients diagnosed with the non-invasive subtype, which reinforces the findings of the present study[11]. For HER-2 positive breast cancer responsive to immunotherapy, the estimates are around 15% for women older than 50 years[12]. Regarding lymphoma, the mean age at the diagnosis is 67 years for non-Hodgkin and 98% of the diagnosed cases are in adults. According to Miller et al.[11], approximately 43% of the patients with this type of cancer receive chemotherapy associated to immunotherapy, as rituximab.

The amount of immunotherapeutics and the diversity of the drugs utilized increased along the decade of 2010-2019 in Barbacena-MG. Until 2015, immunotherapy in the city was limited to BCG and interferon alfa-2B with only two patients utilizing trastuzumab. From 2016 on, a great number of drugs was integrated as for example rituximab and pazopanib. And eventually in 2018-2019, brentuximab, imatinib, denosumab, bevacizumab and cetuximab were included, reaching ten different types of immunotherapies. The raising use of immunotherapeutics along the decade in Barbacena-MG follows a world trend and reflects the necessity of diversification of the oncologic treatments and the concentration in the development of specific target-therapies that has been proven to be more effective and safe in comparison with conventional therapies with reduction of the risk of recurrence of the disease through the stimulation of antitumor memory[8,13]. Likely, along the time, with the progress and increase of manuscripts and trials in this area, the use of immunotherapy either isolated or not can ensure a personalized treatment and improve global and progression free survival of many patients[14]. Once evidences are consolidated, the results of these consistent trials will contribute to increasing integration of immunotherapeutics into SUS, expanding the access to this class of drugs.

Among the immunotherapeutics utilized, the biological modifiers, the monoclonal antibodies and the inhibitors of protein kinase stand out represented by BCG, trastuzumab and imatinib. The first agent proved worldwide was the biological modifier interferon-alfa 2 (IFN-a2) in 1986. BCG was approved by the Food and Drug Administration (FDA) in 1990, aimed to treat non-invasive stage Tis, Ta and T1[15] gall bladder carcinoma and its first use in Brazil as cancer treatment occurred in 2006[16]. The monoclonal antibodies are modified proteins derived from a same clone of lymphocyte B aimed at to target a specific part of deregulated signals transduction pathways in cancer or interfere with immunological processes[3]. In 1999, the FDA approved the utilization of the monoclonal antibody to treat metastatic breast cancer. However, only in 2006 this medication was internationally indicated as adjuvant treatment for this type of cancer[17]. In Brazil, only in 2017, SUS introduced the medication as first line treatment for HER-2 positive metastatic breast cancer[18]. Finally, the class of inhibitors of protein kinase as imatinib that block the action of cellular proliferation and the apoptosis because it prevents the transduction of energetic signs[19]. In 2001, it was integrated to be used in Brazilian public institutions[20] in the same year of FDA approval[21].

During the treatment, 17.8% of the sample analyzed died. Because of few patients using these drugs, it was not possible to evaluate the relation between the efficacy of the therapeutic strategy adopted and mortality. Likely, deaths were not exclusively related to the use of these immunotherapeutics, but also to the histological type of the tumor, staging, age and associated comorbidities.

Of all the treatments conducted in the period, SUS funded 77.9%. The effects of immunotherapeutics in the public health system have been extensively discussed and need to be dealt with attention[7]. The costs of the cancer therapies are raising exponentially and for the next years it is estimated a scenario that can jeopardize the access to oncologic treatment. Due to the high cost of the drugs, the challenge of sustainability of access to these drugs is not only an issue for developing countries, but to any developed country. In Brazil, biological drugs are responsible for high percentage of purchases of the Health Ministry not only because of the recent integration of these products as therapeutic option, but also to the aggregate value of this class of medications[8].

BCG presented mean of treatment of three months consistent with the current litetature[22]. A meta-analysis conducted by Niraula and Gyawali[23] demonstrated that trastuzumab can be used for nine weeks, six months or one year, depending on the protocol followed, corroborating the variation encountered in the present study[23]. The median treatment time with rituximab was seven months, which corresponds to what was found in other countries where the mean of utilization of this immunotherapeutic was within four weeks and 12 months[24]. The variations noticed in the time of treatment reinforce the individualization of the immunotherapy as result of the combination of therapeutic response and toxicity in each patient.

Only patients diagnosed and treated in the oncology reference hospital of the region were enrolled in the study which was a limitation for a more accurate analysis of the use of these medication in the geographical context since it is possible that other patients referred to the hospital might have been submitted to this therapy. On the other hand, this study evaluated the immunotherapeutics integrated in the routine of the institution in Barbacena-MG, an unprecedent and still incipient approach in the Brazilian literature so far.

CONCLUSION

In the last decade, 4.9% of the oncologic patients were treated with immunotherapy in Barbacena-MG. Most of the patients were older than 50 years; BCG was the most prevalent treatment for gall bladder cancer and 17.8% of the patients died during the treatment. Along the years, new immunotherapeutics were incorporated; in the last two years alone, 2018 and 2019, five of the ten immunotherapeutics utilized in the entire decade were incorporated. The improvement and survey of new oncologic therapeutic options have been continuous and justifiable for this treatment to be offered comprehensively to promote health with quality.

CONTRIBUTIONS

All the authors contributed equally for the conception and/or study design, collection, analysis and interpretation of the data, wording and critical review. The authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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