BRIEF REPORT

CHARACTERISTICS OF ONCOLOGICAL CLINICAL TRIALS SUBMITTED TO THE INSTITUTO NACIONAL DE SALUD DEL PERU, 1995-2019

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ABSTRACT

A descriptive observational study was carried out to identify the characteristics of the oncological clinical trials submitted to the Instituto Nacional de Salud del Perú during the period from 1995 to 2019. The information was obtained from the Peruvian Registry of Clinical Trials. We identified 1,996 clinical trials during the studied period, from which 470 were oncological (23.5%); 74.9% of the oncological clinical trials were mainly sponsored by the pharmaceutical industry, 61.9% were phase III and 86.2% were authorized. Regarding those authorized clinical trials, 55.6% were on chemical research products and 35.9% were on therapeutic indication for breast cancer. The most frequent study designs found were: parallel arm (84.7%), randomized (85.2%) and blinded (51.0%); the most frequently used main endpoint was the objective response rate (46.7%). We conclude that the number of oncological clinical trials has been increasing over the years, often with different characteristics.

Keywords: Study Characteristics; Neoplasms; Clinical Trial (Source: MeSH NLM).

INTRODUCTION

Clinical trials (CT) that address oncological issues have found a favorable scenario to evaluate effective therapeutic and/or palliative treatment alternatives, taking into account the different stages of the disease [1]. This is because, cancer is currently considered a global public health problem [2].

Some CT regulatory agencies, beyond their well-known functions of providing the legal framework and safeguarding the integrity of research subjects, have implemented open databases with information on all the CTs they register and authorize. In this regard, the World Health Organization (WHO) manages the International Clinical Trials Registry Platform (ICTRP) https://apps.who.int/trialsearch/Default.aspx), in order to ensure free access to information [3].

This and other databases that consolidate information on CTs around the world have been the subject of research that seeks to identify how the frequency of CTs around the world has varied. Viergever *et al.* identified a steady increase in the number of reported CTs, from 3,294 in 2004 to 23,384 in 2013, although these figures include all types of CTs (oncological and non-oncological) [4].

In Peru, the Instituto Nacional de Salud (INS), as the regulatory authority for clinical trials in the country, has been operating the Peruvian Registry of Clinical Trials (REPEC) since 2007. This database has been used by previous studies to characterize CTs. According to the general report by Minaya *et al.* for the period 1995-2012 [5] and by Alarcón Ruiz et al. for 1995-2017 [6], it is known that cancer-related CTs are the most frequent in the country.

Cite as: Cahuina-Lope P, Solis-Sánchez G, Espíritu N. Characteristics of oncological clinical trials submitted to the Instituto Nacional de Salud del Peru, 1995-2019. Rev Peru Med Exp Salud Publica. 2020;37(4):739-45. doi: https://doi.org/10.17843/rpmesp.2020.374.5167

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Received: 27/01/2020
Approved: 05/08/2020
Online: 09/11/2020

Although these are public databases and are available for all researchers, it was not possible to identify published studies on relevant aspects of the CTs that are oriented to oncological pathologies in Peru. Therefore, the aim of this research was to identify the characteristics of oncological clinical trials (OCT) reported in a 25-year period (1995 to 2019).

KEY MESSAGES

Motivation for the study: In Peru, clinical trials are presented for the evaluation of pharmaceutical products and medical devices in different specialties. The increase in the number of oncological trials is caused by an increase in the global prevalence of cancer. Therefore it, is necessary to determine the characteristics that these trials have had during the last 25 years.

Main findings: There is a variation in the number of clinical trials presented. We observed an increase in oncological trials, most of them sponsored by the pharmaceutical industry and mainly focused on the most prevalent types of neoplasms such as breast cancer.

Implications: Knowledge of the characteristics of oncological clinical trials will allow health professionals to identify the direction in which therapeutic development is headed.

THE STUDY

We carried out an observational and descriptive study to evaluate the characteristics of oncology-related clinical trials that were submitted to the General Office of Research and Technology Transfer (OGITT) of the INS for evaluation and authorization between 1995 and December 31, 2019. The public information found in the REPEC was reviewed and freely accessed through the portal https://ensayosclinicos-repec.ins.gob.pe; the last review was carried out on January 3, 2020. The records found were collected in a database for analysis.

The variables evaluated in the OCTs were grouped into general, design, and studied product characteristics. The general characteristics included type of sponsor, trial status, number of Research Ethics Committees (RECs) that approved the OCT, and number of research centers where the study was conducted.

Sponsors were grouped into five categories: cooperative groups (research networks, scientific societies, civil associations, foundations and research organizations), pharmaceutical industry (industries, laboratories and companies), national health institutes (both in Peru and abroad) and universities (public and private, national and foreign). The status of the trials were grouped into three categories: authorized (active, partial suspension, early termination, finished, suspended after authorization, canceled), unauthorized and others (process without effect, suspended before obtaining authorization, declared in abandonment, declared as withdrawal, declared unsuitable, under evaluation).

Regarding design characteristics of the OCTs, we considered phase of the trial, the specific design, type of blinding, type of randomization and the main endpoint. Regarding the studied product's characteristics, we considered the type of product and the medical indication.

Design and studied product's characteristics were analyzed in all OCTs submitted and in those authorized. Data not found were considered as "not registered" (NR).

Data collected was evaluated with the statistical program Stata V16.1 (Stata Corporation, College Station, Texas, USA) and qualitative variables were described with descriptive summary measures of proportions (%). No statistical imputation processes or inferential tests were carried out.

This study did not require the approval of an ethics committee, since it was a secondary analysis of a free access-database, and because it did not contain data that could identify the subjects.

FINDINGS

We identified 1,996 CTs from the period 1995-2019, of which 470 were oncological (23.5%); the first records were submitted in 1999 (n = 8; 1.7%). The number of CTs varies per year; it was evident that between 1999 and 2002 there were less than 20 per year. Then we observed a constant increase until 2008, when the maximum peak occurred (n = 50; 10.6%) and after this year the number of CTs progressively decreased in the following years. In spite of this, the proportion of OCTs submitted, with respect to the total number of CTs, has increased during the evaluated period (Figure 1).

Regarding the general characteristics of the OCTs, we found that the most frequent type of sponsor was the pharmaceutical industry (74.9%). Most OCTs were authorized (n = 405; 86.2%), of which 61.2% were finished (n = 248). Nearly half (49.6%) of the OCTs were approved

https://doi.org/10.17843/rpmesp.2020.374.5167

by only one REC and the most frequent (n = 249; 26.7%) was the one from the Instituto Nacional de Enfermedades Neoplásicas (INEN). Most of the OCTs (38.1%) were conducted in only one research center. The highest number of research locations for a single study was 14 (Table 1). The proportion of authorized OCTs varied over the years, with a tendency towards an irregular decrease (Supplementary material).

Regarding the design characteristics, most of the OCTs were in phase III, followed by phase II; the most used specific design was parallel groups (84.5%), adaptive CTs were the least frequent ones (basket = 0.4%, umbrella = 0.2). Among the authorized OCTs, open-label and double-blind CTs were found in similar frequency (47.9 and 46.4%, respectively); 85.2% were randomized (Table 2).

During the analysis of the studied product's characteristics, we found that chemical products were the most frequent among the authorized OCTs (55.6%). Regarding the indication of the product, we found that most were therapeutic (91.4%) and those aimed at breast cancer (35.9%) stand out. Among those with palliative indications, products for emesis (45.7%) and pain (34.3%) were the most frequent. The most used main endpoint was the objective response rate, which was used in 47.0% of all the trials and 46.7% among those authorized (Table 3).

DISCUSSION

We identified that the number of OCTs submitted has varied annually. However, considering the proportion of OCTs with respect to the total number of registered CTs, an upward trend was evident, by 2019 these represented almost 50%. This behavior is not specific to Peru, according to the data registered in ClinicalTrials.gov and EudraCT, we found similar distributions in other countries [7].

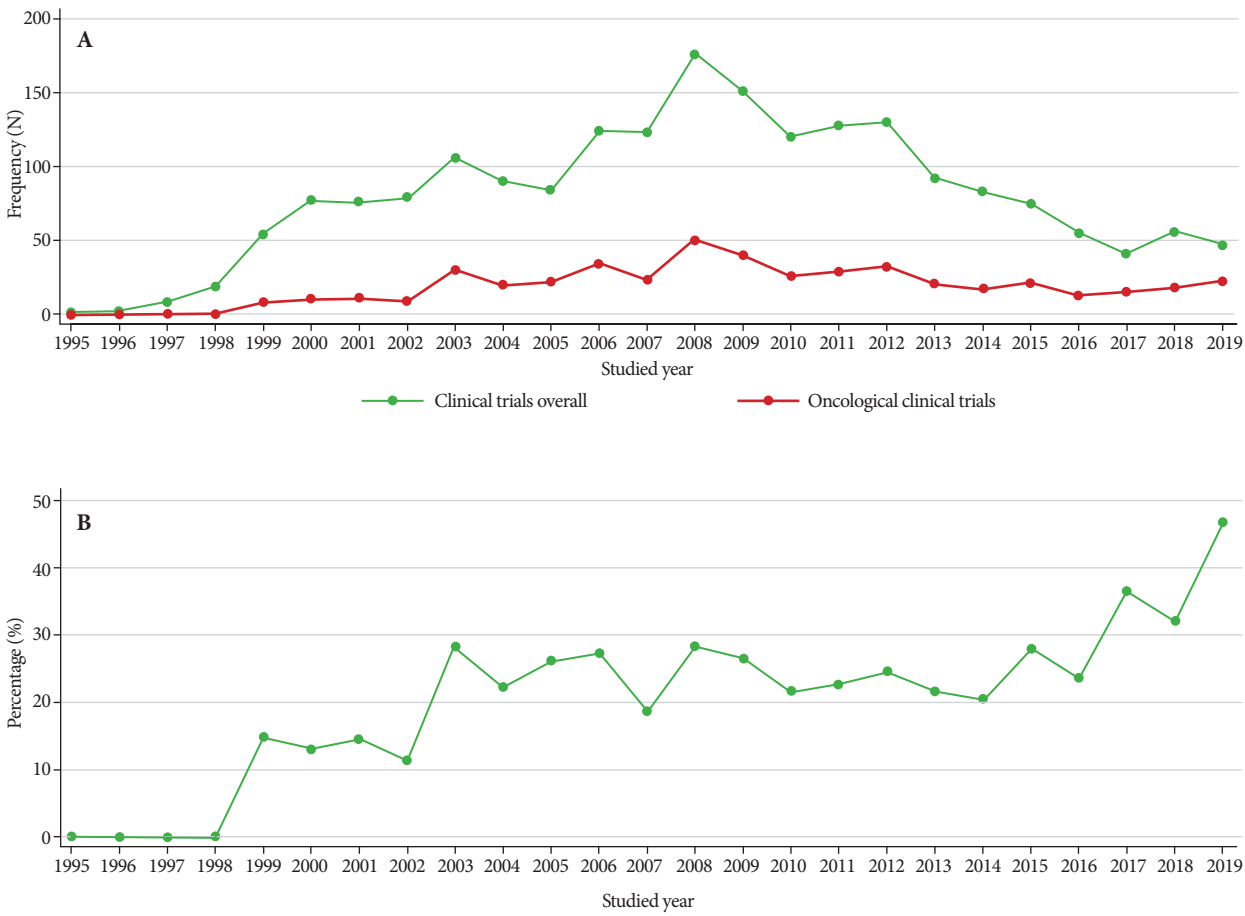

Figure 1. A. Frequency of clinical trials overall and oncological trials presented according to the year studied. **B.** Proportion of oncological clinical trials according to year during the period 1995-2019.

Table 1. General characteristics of oncological clinical trials presented during the period 1995-2019.

Characteristics	n (%)
Type of sponsor	
Cooperative groups	54 (11.5)
Pharmaceutical Industry	352 (74.9)
National Institutes of Health	5 (1.1)
Universities	2 (0.4)
Other	3 (0.6)
NR	54 (11.5)
Status of the trial	
Authorized	405 (86.2)
Active	88 (18.7)
Partial suspension	1 (0.2)
Early termination	13 (2.8)
Finished	248 (52.8)
Suspended after authorization	48 (10.2)
Canceled	7 (1.5)
Unauthorized	18 (3.8)
Other	47 (10.0)
Process without effect	13 (2.8)
Suspended before obtaining authorization	4 (0.9)
Declared in abandonment	10 (2.1)
Declared as withdrawal	13 (2.8)
Declared unsuitable	1 (0.2)
Under evaluation	6 (1.3)
Number of RECs that approved the protocol	
1	233 (49.6)
2	0 (0.0)
3	101 (21.5)
4	78 (16.6)
5	37 (7.9)
6	15 (3.2)
7	3 (0.6)
8	2 (0.4)
9	1 (0.2)
Number of research centers	
1	179 (38.1)
2	81 (17.2)
3	70 (14.9)
4	49 (10.4)
5	36 (7.7)
6	18 (3.8)
7	14 (3.0)
8	10 (2.1)
9	5 (1.1)
10	3 (0.6)
11	2 (0.4)
12	0 (0.0)
13	1 (0.2)
14	2 (0.4)
Total	470 (100.0)

NR: Not registered
REC: Research Ethics Committee.

Table 2. Characteristics of the design of oncological clinical trials presented and authorized during the period 1995-2019.

Characteristics	Presented n (%)	Authorized n (%)
Trial phase		
I	18 (3.8)	14 (3.5)
I-II	1 (0.2)	1 (0.2)
II	135 (28.7)	119 (29.4)
II-III	1 (0.2)	1 (0.2)
III	289 (61.5)	246 (60.7)
IV	22 (4.7)	20 (4.9)
NR	4 (0.9)	4 (1.0)
Specific design		
Single arm	59 (12.6)	51 (12.6)
Parallel groups	397 (84.5)	343 (84.7)
Cross-sectional	7 (1.5)	6 (1.5)
Factorial	4 (0.9)	2 (0.5)
Adaptative-Basket	2 (0.4)	2 (0.5)
Adaptative-Umbrella	1 (0.2)	1 (0.2)
Type of blinding		
Open-label	222 (47.2)	194 (47.9)
Simple	13 (2.8)	10 (2.5)
Doble	222 (47.2)	188 (46.4)
Triple	5 (1.1)	5 (1.2)
NR	8 (1.7)	8 (2.0)
Type of randomization		
Not randomized	9 (1.9)	7 (1.7)
Randomized	400 (85.1)	345 (85.2)
Does not apply	61 (13.0)	53 (13.1)
Main endpoint		
Quality of life	1 (0.2)	1 (0.2)
Cancer incidence	2 (0.4)	2 (0.5)
Report of symptoms	10 (2.1)	10 (2.5)
Safety	23 (4.9)	22 (5.4)
Sensitivity and Specificity	2 (0.4)	2 (0.5)
Overall survival	63 (13.4)	54 (13.3)
Disease-free survival	20 (4.3)	18 (4.4)
Event-free survival	5 (1.1)	5 (1.2)
Progression-free survival	106 (22.6)	89 (22.0)
Complete response rate	8 (1.7)	5 (1.2)
Objective response rate	221 (47.0)	189 (46.7)
Time to Progression	9 (1.9)	8 (2.0)
Total	470 (100)	405 (100)

NR: Not registered

https://doi.org/10.17843/rpmesp.2020.374.5167

Table 3. Characteristics of the studied product of oncological clinical trials presented and authorized during the period 1995-2019.

Characteristics	Presented n (%)	Authorized n (%)
Type of product		
Medical device	3 (0.6)	2 (0.5)
Chemical product	263 (56.0)	225 (55.6)
Biological product	196 (41.7)	172 (42.5)
Other	8 (1.7)	6 (1.5)
Product indication		
Palliative use	38 (8.1)	35 (8.6)
Anemia	3 (7.9)	2 (5.7)
Liver dysfunction	1 (2.6)	1 (2.9)
Intestinal Dysfunction	2 (5.3)	2 (5.7)
Pain	12 (31.6)	12 (34.3)
Emesis	18 (47.4)	16 (45.7)
Hypercalcemia	1 (2.6)	1 (2.9)
Pneumonia	1 (2.6)	1 (2.9)
Therapeutic use	432 (91.9)	370 (91.4)
Anal	1 (0.2)	0 (0.0)
Head and neck	10 (2.3)	7 (1.9)
Brain	1 (0.2)	1 (0.3)
Colorectal	12 (2.8)	9 (2.4)
Cervix	7 (1.6)	4 (1.1)
Esophageal	3 (0.7)	3 (0.8)
Gastrointestinal	24 (5.6)	22 (5.9)
Hematological	32 (7.4)	29 (7.8)
Liver	7 (1.6)	6 (1.6)
Lymphatic	36 (8.3)	28 (7.6)
Breast	148 (34.3)	133 (35.9)
Multiple	13 (3.0)	10 (2.7)
Nasopharyngeal	1 (0.2)	1 (0.3)
Osteosarcoma	1 (0.2)	1 (0.3)
Ovary	10 (2.3)	7 (1.9)
Pancreas	8 (1.9)	6 (1.6)
Skin	10 (2.3)	8 (2.2)
Prostate	28 (6.5)	22 (5.9)
Lung	66 (15.3)	59 (15.9)
Kidney	4 (0.9)	4 (1.1)
Myeloid Sarcoma	2 (0.5)	2 (0.5)
Thyroid	2 (0.5)	2 (0.5)
Uterus	1 (0.2)	1 (0.3)
Vagina and vulva	1 (0.2)	1 (0.3)
Bladder	4 (0.9)	4 (1.1)
Total	470 (100)	405 (100)

In the 25-year period that was analyzed, we found that 23.5% of the CTs were oncological; this figure is similar to the 22.4% reported by Minaya *et al.* [5] for the period 1995-2012. These results show the significant presence of this type of research in our country over time, slightly higher than the 21.8% found in ClinicalTrials.gov for the period 2007-2010 [8].

On the other hand, the studied products were mostly for therapeutic use (91.9%), aimed at the treatment of breast and lung cancer. These findings are consistent with the analysis of Minaya *et al.* [5], and reflect the high incidence of these types of cancer in the world [9]. The high morbimortality of cancer has encouraged the production of OCTs on diagnostic methods, like for example the study of the efficacy of the folate receptor-mediated staining solution as a tool for early detection of cervical cancer [10], or the use of new "digital tomosynthesis" equipment for the systematic identification of breast cancer [11].

Most Peruvian CTs were sponsored by the pharmaceutical industry. A similar pattern is evident in Western European countries, where for the period 2007-2015; 74% of the CTs had commercial sponsorship [12]. Participation of the pharmaceutical industry in the research of new cancer drugs is not something new; this type of financing has already been identified and has shown favorable results in these studies [13].

During the last two years, two new OCTs designs have been registered; these adaptive designs or so-called "Master Protocols", are classified as Basket (defined by cohorts with different types of tumors assigned to the same treatment), and Umbrella (defined by cohorts with the presence of the same type of tumor with or without associated biomarkers that receive different treatments) [14,15]. These adaptive designs, together with the Platform type (not yet registered in our country), have been increasingly adopted worldwide since 2001 as an alternative for OCTs; and are more frequent in the United States [16].

Traditionally, the main endpoints used in the OCTs were clinical improvement measures, such as the improvement of signs and/or symptoms, and the patient's quality of life [17]. However, during the last decade, sponsors have used other criteria to achieve the accelerated approval of anti-cancer drugs, among these we have the tumor shrinkage evaluation and tumor growth retardation [18]. Given this scenario, regulatory agencies have been in charge of evaluating the relevance, case by case, of the use of substitute endpoints and of providing guidelines for reasonable use [19]. All of this

has meant that currently the main endpoints used for these studies are the objective response rate, or progression-free survival, considering that the need for their use will always depend on the context of the disease and the magnitude of the effect, among other factors [20].

A limitation of this study was that the information comes from what was registered in the REPEC, a platform created in 2007, which has been collecting data retrospectively on CTs that had previously been evaluated and authorized by the Ministerio de Salud. This leads to a possible information bias for data from the period 1995-2006. Despite this limitation, this study characterizes the most frequent group of CTs presented in our country in the last 25 years.

In conclusion, the frequency of the OCTs in Peru shows variations during the evaluated period, although proportionally an ascending behavior has been evidenced over the years. It was also possible to identify that phase II and III OCTs are the most frequent in our country. We evidenced that most studied products were for therapeutic use and were aimed at breast cancer.

The identification of OCTs with adaptive designs represents a challenge for ethics committees, patients, researchers and regulatory authorities alike. For this reason, in compliance with its role as the governing body in the area of CTs, the INS is called upon to establish training activities that guarantee an adequate implementation in our country.

Authorship contributions: All authors participated in the conception and design of the article, and in data collection. GS performed the data statistical analysis. All the authors participated in the interpretation of the data, wrote the article, made the critical review of the manuscript and approved its final version.

Funding: Self-funded.

Conflicts of Interest: Paula Cahuina-Lope is coordinator of the clinical trial evaluation team of the Executive Research Office, Nora Espiritu (at the time of submission of the article) was General Director of the General Office of Research and Technology Transfer. Gilmer Solis is an external consultant to the National Institute of Health.

Supplementary material: Available in the electronic version of the RPMESP.

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