BRAZILIAN JOURNAL OF IMPLANTOLOGY AND HEALTH SCIENCES

ISSN 2674-8169

The Efficacy of Oncolytic Viruses in Reducing Neoplasms: A Scoping Review

Maria Eduarda Duarte Maroja[1], Maria Eduarda Gomes de Almeida[1], Manuela Souto Garcia Lavalle[1], Antônio Carlos de Melo Tompson[1], Amanda Cirne Schwartz[1], Kalyel Gomes Muniz[1], Mateus Henrique Dornelles Baz[1], Paulo Gabriel Soares da Silva[1], Hugo Rafael de Souza e Silva[1]

Review Article

ABSTRACT

Abstract: Pancreatic cancer is one of the cancers with the highest mortality rate, largely due to the aggressiveness of the tumor cells and the lack of obvious symptoms at the beginning of the disease. Based on this, the present review aims to analyze the effectiveness of using oncolytic viruses in the treatment of pancreatic neoplasms. To this end, using the PCC research strategy, an acronym for eligibility criteria that means Population, Concept, and Context, the scientific databases PubMed/MEDLINE, LILACS, EMBASE, and ScienceDirect were used. After applying the processes of inclusion, exclusion, selection, data extraction, and assessment of the Level of Evidence, the results were six articles analyzed and used for the scoping review. At the end of the analysis of these articles, two of them detected the DNA of the viruses in the patients' blood, two presented grade I-II adverse events, and two used the same virus. Thus, five of the six articles analyzed demonstrated positive results, with the sixth being considered inconclusive. Therefore, it can be concluded that the treatment of pancreatic neoplasms with the use of oncolytic viruses, depending on the virus and the doses used, presents positive prospects for regression or interruption of the worsening of the disease, proving to be a source of hope for the future.

Keywords: Oncolytic Viruses, Pancreatic Neoplasms, Pancreatic Intraductal Neoplasms, Therapeutics.

A eficácia dos vírus oncolíticos na redução de neoplasias pancreáticas: uma Revisão de Escopo

RESUMO

O câncer de pâncreas é um dos cânceres com mais mortalidade apresentada, muito devido à agressividade das células tumorais, e à falta de aparecimento de sintomas óbvios no início da doença. Com base nisso, a presente revisão tem como objetivo analisar a eficácia da utilização de vírus oncolíticos no tratamento de neoplasias pancreáticas. Para tal, a partir da adoção da estratégia de pesquisa PCC, acrônimo de critérios de elegibilidade que significa: Population (População), Concept (Conceito) e Context (Contexto), foram utilizadas as bases de dados científicos PubMed/MEDLINE, LILACS, EMBASE e ScienceDirect. Após a aplicação dos processos de inclusão, exclusão, seleção, extração de dados e avaliação do Nível de Evidência, teve-se como resultados 6 artigos analisados e utilizados para a revisão de escopo. Ao fim da análise desses artigos, dois deles detectaram o DNA dos vírus no sangue dos pacientes,dois apresentaram eventos adversos de grau I-II e dois utilizaram o mesmo vírus. Assim, 5 dos 6 artigos analisados demonstraram resultados positivos, sendo o 6° considerado inconclusivo. Dessa forma, pode-se concluir que o tratamento de neoplasias pancreáticas com uso de vírus oncolíticos, a depender do vírus e das doses utilizadas, apresenta perspectivas positivas de regressão ou interrupção do agravo da doença, se mostrando como uma fonte de esperança para o futuro.

Palavras-chave: Vírus oncolíticos, Neoplasias Pancreáticas, Neoplasias Intraductais Pancreáticas, Tratamento

Instituição afiliada – FACULDADE DE CIÊNCIAS MÉDICAS- UNIVERSIDADE DE PERNAMBUCO
Dados da publicação: Artigo recebido em 02 de Maio e publicado em 22 de Junho de 2024.
DOI: https://doi.org/10.36557/2674-8169.2024v6n6p1587-1605

Autor correspondente*: Paulo Gabriel Soares da Silva* E-mail do autor: paulo.gabriel@upe.br

INTRODUCTION

Pancreatic cancer is one of the cancers with the highest mortality rates, due to the fact that patients don't show obvious symptoms during the development of the disease, the tumor cells are very invasive and early diagnosis is highly difficult, in addition, the disease has a considerable recurrence even after radical treatment [1] .

The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma, which develops from intraepithelial neoplasms and intraductal papillary mucinous neoplasms, considered to be potentially cancerous hyperplastic lesions [2] .

In this respect, it is necessary to elucidate the epidemiology of this disease. In the global scenario, it is possible to observe an increase in the number of new cases of this type of pathology in the last two decades: in 2017, 441,000 cases were recorded, compared to 196,000 cases in 1990, which represents an approximately twofold increase in the number of pancreatic cancer cases in the aforementioned period [3] . In addition, it is worth noting that in 2020 there were approximately 495,000 cases and 466,000 deaths, which represents 2.6% and 4.7% respectively of the total number of cases and deaths of all types of cancer [4] . In addition, the highest incidences of the disease are 9.9 per 100,000 males in Eastern Europe and 7.4 per 100,000 females in Western Europe [4] .

In this sense, the main risk factors for the disease include both non-modifiable ones, such as age over 55, male gender, genetic factors predisposing to cancer, and diabetes, and modifiable factors, such as tobacco consumption, alcohol, obesity and chronic pancreatitis[5].

It is worth noting that the main treatments for pancreatic cancer include surgery - resection of the tumor or partial removal of the pancreas, with the first option not being recommended in all cases, given that only 15 - 20% of patients diagnosed with pancreatic ductal adenocarcinoma are eligible for resection, since the choice of this therapeutic method depends on the tumor location and patients already have distant metastases, combined with the fact that the pancreas is close to critical blood vessels [6,7] . In view of this, it is worth noting that partial removal of the pancreas causes loss of some functions in both digestion and systemic metabolism linked to the endocrine part

of the organ, in view of the complications related to this type of removal, among which we can highlight: ischemic complications (porto-mesenteric venous thrombosis), infections (pancreatitis), delayed gastric emptying and fistulas[8] .

Meanwhile, clinical treatment is chemotherapy, which is independent of eligibility for surgery, and generally uses two combinations of the following chemotherapy drugs: 5- fluorouracil, leucovorin, irinotecan and oxaliplatin; while the other therapeutic regimen consists of a combination of gemcitabine with nab-paclitaxel; it is a therapy used with palliative intent in patients with unresectable malignant tumors that have metastasized to other sites [6,9] .

In view of the above, which reveals the complexity of pancreatic cancer treatment, treatment with oncolytic viruses has emerged as an interesting and innovative alternative on the medical scene. This is a revolutionary technique, and for over a century results have been seen in the regression of cancer when infected with certain types of specific viruses[10] .

In this context, the oncolytic virus is a genetically manipulated agent, but it can also be found in nature, which replicates selectively and manages to kill cancer cells without affecting normal tissues [11]. Treatment with oncolytic viruses is an interesting alternative because it has good efficacy, few adverse effects and, when compared to chemotherapy and radiotherapy, is less painful for the patient, and has the advantage that the clinical trials carried out to date have not shown any deaths or serious adverse effects resulting from the use of these viruses in tumor therapy [10].

In view of the above, this topic is extremely important due to the therapeutic difficulties encountered with pancreatic neoplasms. The aim of this study is to map publications on the use of oncolytic viruses in the treatment of patients with pancreatic neoplasms, in the clinical outcome of remission of this type of neoplasm, as an alternative to conventional treatments or even acting in conjunction with chemotherapeutic agents. This could lead to the discovery of a more effective and less aggressive way of treating pancreatic cancer, providing patients with a better quality of life.

METHODOLOGY

The study carried out is a scoping review used to analyze the scope of the available literature and the state of the art on a particular topic or issue [12] . In addition,

this type of study serves as a basis for determining the value and suitability for structuring a systematic review, in addition to contributing to identifying gaps on certain scientific topics in the existing literature [13].

This review followed the guidelines proposed by PRISMA-scr, a checklist that aims to help authors develop a better understanding of the basic concepts and the main items to be reported in a study of this type [14] .

From this perspective, to guide the search strategy with the aim of broad and accurate data collection, the PCC strategy was used, an acronym for eligibility criteria which stands for: Population, Concept and Context [15] . Therefore, the following research question was formulated: "What is the efficacy of oncolytic virus therapy for the treatment of pancreatic neoplasms in the clinical outcomes of cancer remission?".

The protocol for this review was registered in the Open Science Framework (OSF) system, under the registration number https://doi.org/10.17605/OSF.IO/8P3BY.

Inclusion Criteria

The inclusion criteria defined were: articles published between December 2013 and December 2023, free articles, articles written in English, Spanish or Portuguese, articles relating oncolytic viruses to the treatment of pancreatic neoplasms. Furthermore, types of studies were determined for the inclusion of articles in the development of the review, established as: Randomized Clinical Trials, Non-Randomized Clinical Trials, Prospective and Retrospective Studies, Case-Control Studies and Observational Studies.

Exclusion Criteria

The exclusion criteria defined were articles which, despite having part of the descriptors in their structure, did not correspond to the aim of this scoping review, such as other types of treatment not related to immunotherapy or non-pancreatic neoplasms. In addition, those that did not fit into one of the previously defined types of articles were excluded.

Search strategy

The databases used for this study were: *Medline/PubMed,* LILACS, *Science Direct* and *Embase* (the latter accessed via the Institutional *login of* the University of Pernambuco), which are reference sources for the health area and have a wide literature produced on the chosen topic

To develop the search strategy in PubMed and LILACS, which was carried out in December 2023, the following were used the "Health Sciences Descriptors" (DeCs) and "Medical Subject Headings" (MeSH) platforms. Finally, the following descriptors were selected: *efficacy, oncolytic viruses, treatment, pancreatic neoplasms*.

For the Science Direct and Embase databases, the descriptors were selected through the Emtree platform. These descriptors were therefore selected: *efficacy, therapy, oncolytic virus, pancreas tumor, pancreatic intraductal neoplasia*.

The descriptors were then put together and each search strategy was drafted for the different databases, as shown in Chart 1.

Chart 1 - Search strategy used in the databases

Database	Search strategies
PubMed/MEDLINE	((((Efficacy) AND (Oncolytic Viruses)) AND (Treatment)) AND (pancreatic neoplasms)) OR (Pancreatic Intraductal Neoplasms)
LILACS	((((Efficacy) AND (Oncolytic Viruses)) AND (Treatment)) AND (Pancreatic Neoplasms)) OR (Pancreatic Intraductal Neoplasms)
BASIS	('pancreatic intraductal neoplasia'/exp OR 'pancreatic intraductal neoplasia' OR 'pancreas tumor'/exp OR 'pancreas tumor') AND ('oncolytic virus'/exp OR 'oncolytic virus') AND ('therapy'/exp OR ' therapy') AND ('efficacy'/exp OR 'efficacy')
ScienceDirect	'oncolytic virus' AND 'pancreatic neoplasm' AND 'efficacy' AND 'Treatment'.

Source: the authors (2024)

Selection procedures

Therefore, based on the review criteria and the selection of articles described, two independent reviewers began to screen the studies found in the databases. Under this bias, articles related to oncolytic viruses and pancreatic neoplasms, as well as the types of study mentioned above, were considered suitable for the purpose of this study. On the other hand, publications which, despite having the previously defined descriptors, did not correspond to the aim of this research were excluded.

In this way, the reviewers read the title and abstract of each article in detail and extensively, with the intention of ensuring that only publications associated with the previously defined criteria were selected.

Data extraction procedures

Therefore, after the article selection phase, three independent reviewers carried out the data extraction phase. At this point, a file was created in table format using the free Google Spreadsheets *software*, using the institutional access @upe.br. Where the following data was used in the formatted table: authors, language, year of publication, objective, methodology, results, conclusions/recommendations and type of article.

Evaluation of the Level of Evidence

In order to assess the Level of Evidence of the studies included in this study, it was necessary to implement the methodology based on the *Oxford Center for Evidence-based Medicine* method (Chart 2). This approach classifies the various studies found in the literature into levels of evidence which vary in the following values: 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4 and 5, where 1a indicates studies with good quality evidence, while level 5 represents those opinions lacking critical evaluation or based on basic material [16].

Chart 2 - Levels of Evidence for scientific studies

Degree	Level of Evidence	Treatment/Prevention	Diagnosis
A	1A	Systematic Review (with homogeneity) of controlled and randomized clinical trials	Systematic review (with homogeneity) of level 1 diagnostic studies criteria of level 1B studies, in different clinical centers
	1B	Randomized controlled clinical trials with narrow confidence intervals	Cohort validated with good reference standard diagnostic criteria tested in a single center.
	1C	"All or nothing" therapeutic result	Sensitivity and specificity close to 100%.
B	2A	Systematic Review (with homogeneity) of Cohort Studies	Systematic Review (with homogeneity) of diagnostic studies at level > 2.
	2B	Cohort Study (including Lower Quality Randomized Clinical Study)	Exploratory cohort with good reference standard diagnostic criteria derived or validated in samples or databases.

	2C	Observation of Therapeutic Results (outcomes research) and/or Ecological Study	
	3A	Systematic Review (with homogeneity) of Case-Control Studies	Systematic Review (with homogeneity) of diagnostic studies at level > 3B.
	3B	Case-Control Study	Non-consecutive selection of cases, or reference standard applied in a inconsistent manner
C	4	Case Reports (including Cohort or Case-Control of lower quality)	Case-control study or poor or non-independent reference standard.
D	5	Expert opinion without critical evaluation or based on basic materials (physiological study or animal study)	

Source: The authors (2024)

RESULTS

In the database known as PubMed/MEDLINE, 4676 articles were initially found, and after the first search filter, referring to the free text, 1524 studies remained, after the second filter, corresponding to the publication date of the article (defined for studies published in the last 10 years, that is, in the period between December 2013 and December 2023), 1056 studies were found, and finally, after the last filter, carried out with the filter "clinical trials" and "randomized controlled trial", 20 trials were selected.

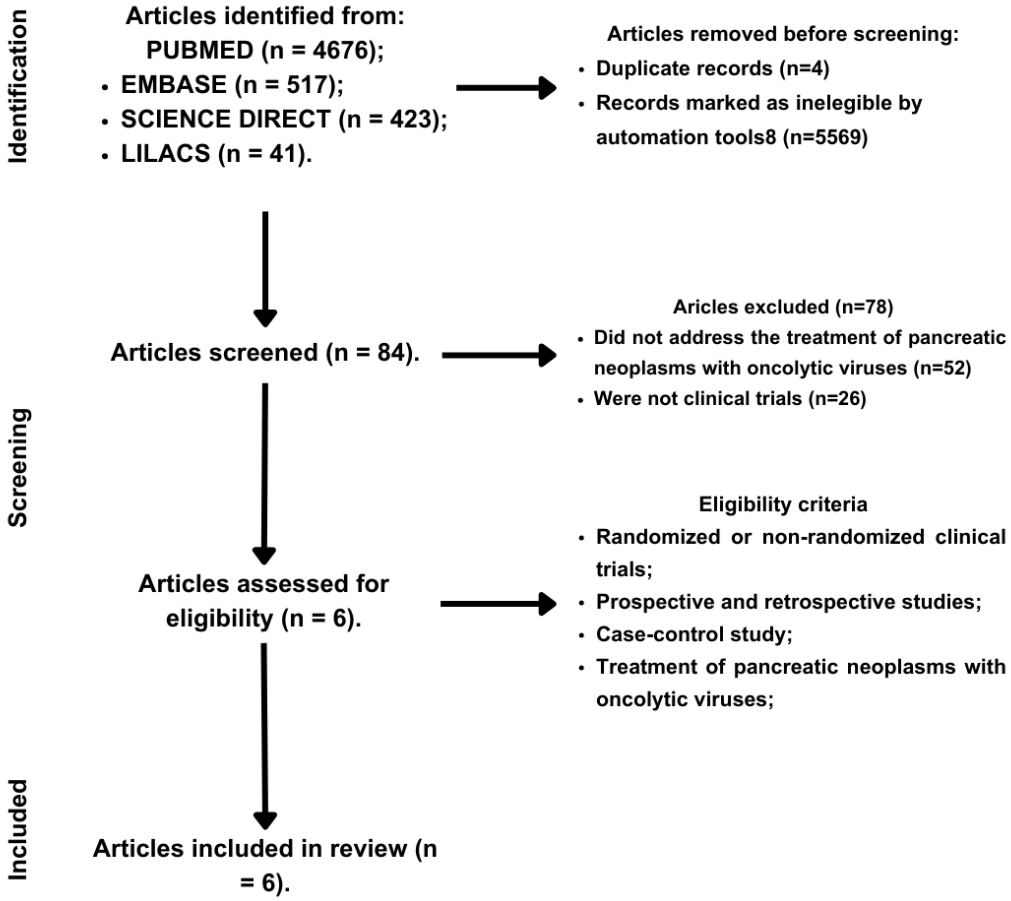
The primary search in the Latin American and Caribbean Health Sciences Literature (LILACS) database resulted in 41 studies and, after applying the filter corresponding the date, this number fell to 25 articles and remained after applying the filter corresponding to "free full text". However, it decreased to 17 when the type of study filter was applied, which delimited : diagnostic study, prognostic study and observational study.

In the *Science Direct* data base, *there* were 421 results, and after the first filtering, corresponding to "*open access* & *open archive*", 85 articles remained, in the second filter, which delimited the date, the number of studies was reduced to 66. Finally, by applying the filter based on the type of research carried out (*Research articles*), 16 clinical trials remained.

In the EMBASE database, 576 results were first found. After applying the first filter based on date, 357 articles were found. Finally, the studies were delimited into the following categories: *clinical trial, comparative effectiveness, comparative study*

and randomized controlled trial, leaving 32 results.

From these articles, the selection began with 84 articles, and after detailed reading, only 6 remained and 78 studies were excluded, as they did not fit the objective of this study, as shown in Figure 1.



Of these articles, all correspond to Clinical Trials. Of these studies, 83.33% (n=5) are non-randomized clinical trials, while 16.67% (n=1) are randomized clinical trials, as shown in Chart 3.

Chart 3 - Types of studies included in the scoping review

Authors and publication date	Kind of study	Level of Evidence
Chawla et al., 2018 [17]	Non-randomized clinical trial	2B
Barton et al., 2020 [18]	Non-randomized clinical trial	2B
Mahalingam et al., 2019 [19]	Non-randomized clinical trial	2B
Bazan-Peregrinoet al., 2021 [20]	Non-randomized clinical trial	2B

Noonan et al., 2016 [21]	Randomized clinical trial	1B
Musher et al., 2020 [22]	Non-randomized clinical trial	2B

Source: The authors (2024)

The articles are similar in terms of their methodology, as they all evaluate the efficiency of the activity of oncolytic viruses in the treatment of pancreatic adenocarcinoma, as well as their ability to prevent tumor growth through intravenous or tumor administration, although they differ in the type of virus used.

The studies used an analysis of a randomly selected group to evaluate different reactions to the use of the oncolytic virus. In the studies selected, the population analyzed corresponded to the eligibility criteria defined in each study.

In the phase I-II study using Rexin-G[17], treatment with Rexin-G (Retroviral Expression Vectors Bearing Inhibitory Genes) was evaluated in which all patients had metastatic Pancreatic Ductal Adenocarcinoma (PDAC) and had failed a median of two treatment regimens prior to the study. The Rexin-G vector has as its result a biological potency of 50 to 70% of the growth inhibitory activity of target cancer cells. The vector prepared for infusion was administered intravenously at 4 ml/min. There were 20 patients, 15 of whom received a full course of treatment (4 weeks). 2 patients had 1 target lesion for Rexin-G and 17 had 2 to 7 target lesions in the pancreas, lymph nodes, omentum, mesentery and adrenal glands, bone, lung and liver (the latter in 16 patients). However, many had non-target lesions, such as malignant ascites, pleural effusion and peritoneal carcinomatosis, so the number of target lesions alone does not reflect the patient's total tumor burden. Related but not clinically relevant reactions were reported by 7 patients. These were: chills (1 patient), fatigue (2 patients), headache after level II dosing (1 patient) and after level III dosing (4 patients). No patient tested positive for: Rexin-G vector neutralizing antibodies, antibodies to gp70 (collagen receptor on the capsule that captures abnormal Signature [SIG] proteins in the tumor microenvironment). 19 of the 20 patients died, but from causes unrelated to the Rexin-G treatment. It was observed that the final product was a biological potency, which corresponds to a viral multiplicative capacity and amplification of the lytic process in tumor cells[18] of 50-70% in the 20 patients evaluated and, therefore, Rexin-G exhibits dose-dependent antitumor activity in patients with gemcitabine refractory PDAC metastasis[17] .

In one of the selected studies[19] , the safety of using a replication-competent

oncolytic adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12), expressing kCD/mutT KSR39 yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase, and gene therapy with interleukin-12 (IL12) in patients with pancreatic cancer was evaluated. Twelve patients received Ad5- yCD/mutTKSR39-rep-hIL-12 and oral 5-Fluorocytosine (5-FC). In addition, subjects received 5-FC therapy for 7 days, followed by chemotherapy (FOLFIRINOX or albumin-bound gemcitabine/paclitaxel), starting 21 days after adenovirus injection. The study endpoint was toxicity occurring during day 21. Experimental endpoints included measurements of IL12, interferon gamma (IFNG) and CXCL10 to assess immune system activation. In addition, peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. 94% of the 121 adverse events were grade I-II, without the need for medical intervention. The study was carried out with 12 patients, but DNA from Ad5- yCD/mutTKSR39rep-hIL-12 was only detected in 2 patients. High levels of serum IL12, IFNG and CXCL10 were detected in 42%, 75% and 92% of subjects, respectively. Analysis of the immune cell population indicated activation after administration of Ad5- yCD/mutTKSR39rep-hIL-12. Thus demonstrating an anti-tumor capacity related to the virus[19]

In the phase Ib single-arm clinical trial developed by Mahalingam et al, *Pembrolizumab in Combination with the Oncolytic Virus Pelareorep and Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma: A Phase Ib Study*[20] , the efficacy of pelareorep in combination with pembrolizumab and chemotherapy in patients with PDAC who progressed after first-line treatment was analyzed. The use of pelareorep (oncolytic reovirus), combined with pembrolizumab and 5-fluorouracil, gemcitabine or irinotecan - drugs used in chemotherapy - allowed the disease to be controlled in 3 out of 10 patients. The adverse events observed, mainly grade I-II, were well tolerated. Virus replication was observed in tumor biopsies during treatment and sequencing of peripheral blood T-cell receptors revealed the creation of new clones of these cells during treatment. High peripheral clonality and changes in the expression of immune genes were observed in patients, showing benefits. Thus, the use of pelareorep and pembrolizumab combined with chemotherapy showed no significant toxicity and showed efficacy[20] . Another randomized phase II study by Noonan et al. analyzed the efficacy of pelareorep in the treatment of metastatic pancreatic adenocarcinoma when combined with carboplatin and paclitaxel[21] , drugs commonly used in chemotherapy due to their induction of apoptosis and inhibition of tumor

growth. To analyze, 73 treatment-naive patients were randomized between February 2011 and April 2014, divided into two arms: A (paclitaxel/carboplatin + pelareorep) and B (paclitaxel/carboplatin), with 36 and 37 patients each, respectively. All patients received intravenous infusions of paclitaxel on day 1 of each 21-day cycle at 175mg/m2 for 3 hours followed by carboplatin carboplatinin an area of dose under the concentration-time curve of 5mg/ml/minute over 30 minutes. In Arm A, pelareorep was administered after paclitaxel and carboplatin in intravenous infusion on days 1-5 of each cycle; patients in Arm B could switch to Arm A if the disease progressed. Subsequently, an immunophenotypic analysis was carried out on plasma and peripheral blood mononuclear cells isolated from 70 patients, evaluating pre and post-treatment samples. In this study, the addition of Pelareorep to carboplatin and paclitaxel did not improve progression-free survival (PFS) compared to carboplatin and paclitaxel alone and only 5 of the 73 patients were alive and without disease progression. Thus, Pelareorep and Pembrolizumab showed more efficacy than Pelareorep with carboplatin and paclitaxel together. However, when analyzing immunologically, the study has limitations, since the blood studied was peripheral blood and so, it does not necessarily accurately reflect the microenvironment of the tumor[21]

Bazan-Peregrino and colleagues carried out a study that analyzed the action of VCN- 01 - an oncolytic adenovirus with direct antitumor effects and the ability to disrupt the stroma-, *VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects*[22] . For this purpose, pancreatic xenografts were used after intravenous and intratumoral administration in patients with PDAC . In the research, it was observed that VCN-01 replicates and expresses hyaluronidase after intratumoral injection. This enzyme facilitated tumor extravasation and increased uptake of chemotherapeutic agents and antibodies. Thus, it was seen that SoC chemotherapy (gemcitabine or nab-paclitaxel/gemcitabine) proved to be a strong ally in the treatment, since it reduced tumor growth to a greater extent than both treatments administered separately, leading to complete regression in 80% (8/10) of the tumors. High doses showed a toxicity threshold, but it was observed that the intratumoral injection was well tolerated by the patients participating in the study. In isolation, the virus also showed efficacy both in pre-clinical models and in patients with pancreatic neoplasia. Finally, it was found that better access to chemotherapy and reduced tumor stiffness favor local control of pancreatic tumors treated with CNV-01 in addition to standard treatment. Elastography of tumors treated with VCN-01 showed a reduction in tumor stiffness, regardless of the

coadministration of nab-paclitaxel[22] .

In the *phase* I/II clinical trial by Musher et al. *A phase I/II study of LOAd703, a TMZ- CD40L/4-1BBL-armed oncolytic adenovirus, combined with nab-paclitaxel and gemcitabine in advanced pancreatic cancer*[23] , patients with unresectable or metastatic pancreatic ductal adenocarcinoma (PDAC) were treated with intratumoral injections of LOAd703 and standard intravenous chemotherapy with nab-paclitaxel/gemcitabine (nPG) and standard chemotherapy at different dosages. Three dosage levels of LOAd703 were investigated using a BOIN-type base escalation. The endpoints were safety and feasibility. In patients treated with the highest dose level the objective response rate was 55% (5/11 subjects), thus reaching the pre-defined criterion for efficacy, and in others with lower doses emergent immune responses were observed. Among all patients with an evaluable response, the overall response rate was 44%, and the disease control rate was 94%. The combination of intratumoral LOAd703 injections with standard nPG chemotherapy was safe and feasible. The target response at the highest dose level was achieved and treatment-emergent immune responses were observed[23] .

In all the studies, the results confirmed the use of the oncolytic virus as an ally in the treatment of pancreatic neoplasia, either by suppressing the cancer or preventing it from worsening. Thus, in the studies analyzed, there was a reduction in tumor growth.

DISCUSSIONS

That way, it can be seen that the treatment of this type of neoplasm with oncolytic viruses has shown promise, given that the clinical trials analyzed in this study showed that this therapy was significantly effective in reducing tumors in a considerable number of participants. However, it is worth noting that these studies are still in the early stages of a Clinical Trial (Phases I and II).

It should therefore be noted that Phase I studies are non-therapeutic trials, since they are concerned with examining pharmacokinetic and pharmacodynamic effects, while Phase II studies are exploratory trials, since they examine the effective dose and therapeutic effects on patients, as well as determining the therapeutic regimen and drug interactions24 .

Therefore, based on the researched literature, it is important to note that there is a need to develop more advanced phases (Phases III and IV) of clinical trials on this subject, in order to confirm the efficacy of this therapy, and thus implement it as a

treatment for pancreatic neoplasms.

In addition, it was noted that although the studies dealing with this therapeutic measure were relatively recent, it had also been tested in other types of cancer, showing promising results. For that matter, it is worth noting that the result found by the study on the use of the Rexin-G retroviral vector17 , which demonstrated significant efficacy in the treatment of advanced pancreatic cancer, is corroborated by another article which explores its usefulness in the treatment of sarcoma and osteosarcoma25 , since this virus contributed both to controlling tumor growth and improving survival in both cases.

In addition, one of the studies included in this review20 meets the research of a study that used Pelareorep26. In the first, the drug was combined with pembrolizumab and chemotherapy for patients with advanced pancreatic adenocarcinoma and in the second, with FOLFIRI/bevacizumab in individuals with colorectal cancer with a KRAS mutation, an oncogene that activates signaling cascades involved in tumor proliferation and metastasis. The treatment proved to be safe, effective and promising in both situations.

The study combining Pelareorep with carboplatin and paclitaxel in the treatment of metastatic pancreatic adenocarcinoma21 corroborates another study designed for patients with lung cancer, combining Pelareorep with second-line chemotherapy27 , which added, concluded that the use of the drug is safe and tolerable, but did not promote, in the long term, an improvement in the progression-free survival of patients, requiring further studies into the beneficial potential of the retrovirus.

In addition, another study included in this review23 is in line with the results of the preclinical trial carried out on the efficacy of using LOAd703 in the treatment of tumors28 , since both studies concluded that this technique would be effective, safe and capable of promoting immunomodulatory activity with an anti-tumor effect. However, there is still a need to develop studies in humans that address the efficacy of this virus for the treatment of neoplasms.

Regarding the use of CNV-01, one of the studies22 concluded that the virus has the ability to act effectively on dense stromal neoplasms, which corroborates the conclusions of a clinical trial carried out which indicated the safety and promising anti-tumor effects of CNV- 0129 .

Regarding treatment with Ad5-yCD/mutTKSR39rep-mIL1219 , the study did not reach the maximum tolerated dose and was therefore unable to reach a conclusion.

However, the virus showed encouraging signs of efficacy, which indicates that it is promising for future studies. This is compliant with the results of a preclinical trial30 , which, in the context of prostate cancer, found that the use of this adenovirus is well tolerated, capable of promoting regression of tumor size and indicated for future studies.

Thus, it can be seen that research into some oncolytic viruses is still in its early stages, which suggests that it is a topic that has been little explored in the literature. It is therefore necessary to invest in research to assess the efficacy and safety of this therapeutic method, as well as the adverse effects.

CONCLUSION

Thus, it can be inferred that the present study achieved its objective of scientifically analyzing different studies on the use of oncolytic viruses in the treatment of pancreatic neoplasms.

Therefore, the results of this review were positive, since 5 of the 6 studies analyzed showed positive progress in reducing tumors or stopping their worsening. Despite being phase I and II studies, and in need of progression to phases III and IV, their results are promising and hopeful for medicine. However, it is clear that more studies need to be carried out in order to achieve satisfactory levels of evidence for the treatment of pancreatic cancer.

BIBLIOGRAPHICAL REFERENCES

1. Zhao Z, Liu W. Pancreatic Cancer: A Review of Risk Factors, Diagnosis, and Treatment. Technol Cancer Res Amp Treat [Internet]. Jan 1, 2020 [cited Feb 18, 2024];19:153303382096211. Available from: https://doi.org/10.1177/1533033820962117

2. Grant TJ, Hua K, Singh A. Molecular Pathogenesis of Pancreatic Cancer. Prog Mol Biol Transl Sci [Internet]. 2016 [cited Feb 18, 2024];144:241-275. doi: 10.1016/bs.pmbts.2016.09.008. Epub 2016 Oct 15. PMID: 27865459; PMCID: PMC6260831.

3. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Amp Hepatol [Internet]. May 17, 2021 [cited Feb 18, 2024];18(7):493- 502. Available from: https://doi.org/10.1038/s41575-021-00457-x

4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA [Internet]. Feb 4, 2021 [cited Feb 18, 2024];71(3):209-49. Available from: https://doi.org/10.3322/caac.21660

5. Capasso M, Franceschi M, Rodriguez-Castro KI, Crafa P, Cambiè G, Miraglia C, Barchi A, Nouvenne A, Leandro G, Meschi T, De' Angelis GL, Di Mario F. Epidemiology and risk factors of pancreatic cancer. Acta Biomed [Internet]. 2018 Dec 17 [cited Feb 18, 2024]] . 89(9-S):141-146. Available from: https://pubmed.ncbi.nlm.nih.gov/30561407/

6. Kolbeinsson HM, Chandana S, Wright GP, Chung M. Pancreatic cancer: a review of current treatment and novel therapies. J Investig Surg [Internet]. Oct 3, 2022 [cited Feb 18, 2024]:1-11. Available from: https://doi.org/10.1080/08941939.2022.2129884

7. Halbrook CJ, Lyssiotis CA, Pasca di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. Cell [Internet]. Apr 2023 [cited Feb 18, 2024];186(8):1729-54. Available from: https://doi.org/10.1016/j.cell.2023.02.014

8. Lermite E, Sommacale D, Piardi T, Arnaud JP, Sauvanet A, Dejong CH, Pessaux P. Complications after pancreatic resection: diagnosis, prevention and management. Clin Res Hepatol Gastroenterol [Internet]. Jun 2013 [cited Feb 18, 2024];37(3):230-9. Available from: https://doi.org/10.1016/j.clinre.2013.01.003

9. Springfeld C, Jäger D, Büchler MW, Strobel O, Hackert T, Palmer DH, Neoptolemos JP. Chemotherapy for pancreatic cancer. Presse Medicale [Internet]. Mar 2019 [cited Feb 18, 2024];48(3):e159-e174. Available from: https://doi.org/10.1016/j.lpm.2019.02.025

10. Mondal M, Guo J, He P, Zhou D. Recent advances of oncolytic viruses in cancer therapy. Hum Vaccines Amp Immunother [Internet]. 20 Feb 2020 [cited 18 Feb 2024];16(10):2389-402. Available from: https://doi.org/10.1080/21645515.2020.1723363

11. Fukuhara H, Ino Y, Todo T. Oncolytic virus therapy: a new era of cancer treatment at dawn. Cancer Sci [Internet]. Sep 9, 2016 [cited Feb 18, 2024];107(10):1373-9. Available from: https://doi.org/10.1111/cas.13027

12. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol [Internet]. Feb 2005 [cited Feb 3, 2024];8(1):19-32. Available from: https://doi.org/10.1080/1364557032000119616

13. Thomas A, Lubarsky S, Durning SJ, Young ME. Knowledge syntheses in medical education. Acad Med [Internet]. Feb 2017 [cited Feb 3, 2024];92(2):161-6. Available from: https://doi.org/10.1097/acm.0000000000001452

14. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MD, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA extension for scoping reviews (prisma-scr): checklist and explanation. Ann Intern Med [Internet]. Sep 4, 2018 [cited Feb 3, 2024];169(7):467. Available from: https://doi.org/10.7326/m18-0850

15. Oliveira Araújo WC. Health information retrieval. Converg Em Cienc Informacao [Internet]. Jul 10, 2020 [cited Feb 3, 2024];3(2):100-34. Available at: https://doi.org/10.33467/conci.v3i2.13447

16. Galvão TF, Pereira MG. Assessing the quality of evidence from systematic reviews. Epidemiologia Serv Saude [Internet]. Mar 2015 [cited Feb 3, 2024];24(1):775-8. Disponível em: https://doi.org/10.5123/s1679-49742015000100019

17. Chawla SP, Bruckner H, Morse MA, Assudani N, Hall FL, Gordon EM. A Phase I-II Study Using Rexin-G Tumor-Targeted Retrovector Encoding a Dominant-Negative Cyclin G1 Inhibitor for Advanced Pancreatic Cancer. Mol Ther Oncolytics [Internet]. Mar 2019 [cited 2024 Mar 1];12:56-67. Available from: https://doi.org/10.1016/j.omto.2018.12.005

18. Costanzi-Strauss E, Strauss BE. Perspectives on gene therapy. Rev Medicina [Internet]. 22 Dec 2015 [cited 1 Mar 2024];94(4):211. Disponível em: https://doi.org/10.11606/issn.1679-9836.v94i4p211-222

19. Barton KN, Siddiqui F, Pompa R, Freytag SO, Khan G, Dobrosotskaya I, Ajlouni M, Zhang Y, Cheng J, Movsas B, Kwon D. Phase I Trial Of Oncolytic Adenovirus-Mediated Cytotoxic And Interleukin-12 Gene Therapy For The Treatment Of Metastatic Pancreatic Cancer. Mol Ther Oncolytics [Internet]. Dec 2020

[cited 1 Mar 2024]. Available from: https://doi.org/10.1016/j.omto.2020.11.006

20. Mahalingam D, Wilkinson GA, Eng KH, Fields P, Raber P, Moseley JL, Cheetham K, Coffey M, Nuovo G, Kalinski P, Zhang B, Arora SP, Fountzilas C. Pembrolizumab in Combination with the Oncolytic Virus Pelareorep and Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma: A Phase Ib Study. Clin Cancer Res [Internet]. Nov 6, 2019 [cited March 1, 2024];26(1):71-81. Available from: https://doi.org/10.1158/1078-0432.ccr-19-2078

21. Noonan AM, Farren MR, Geyer SM, Huang Y, Tahiri S, Ahn D, Mikhail S, Ciombor KK, Pant S, Aparo S, Sexton J, Marshall JL, Mace TA, Wu CS, El-Rayes B, Timmers CD, Zwiebel J, Lesinski GB, Villalona-Calero MA, Bekaii-Saab TS. Randomized Phase 2 Trial of the Oncolytic Virus Pelareorep (Reolysin) in Upfront Treatment of Metastatic Pancreatic Adenocarcinoma. Mol Ther [Internet]. Jun 2016 [cited 1 Mar 2024];24(6):1150-8. Available from: https://doi.org/10.1038/mt.2016.66

22. Bazan-Peregrino M, Garcia-Carbonero R, Laquente B, Álvarez R, Mato-Berciano A, Gimenez-Alejandre M, Morgado S, Rodríguez-García A, Maliandi MV, Riesco MC, Moreno R, Ginestà MM, Perez-Carreras M, Gornals JB, Prados S, Perea S, Capella G, Alemany R, Salazar R, Blasi E, Blasco C, Cascallo M, Hidalgo M. VCN-01 disrupts pancreatic cancer stroma and exerts antitumor effects. J Immunother Cancer [Internet]. Nov 2021 [cited 1 Mar 2024];9(11):e003254. Available from: https://doi.org/10.1136/jitc-2021-003254

23. Musher BL, Smaglo BG, Abidi W, Othman M, Patel K, Jing J, Stanietzky N, Lu J(, Brisco A, Wenthe J, Brenner B, Eriksson E, Leen AM, Hilsenbeck SG, Ullenhag GJ, Rowinsky EK, Grilley B, Loskog AS.A phase I/II study combining a TMZ-CD40L/4-1BBL-armed oncolytic adenovirus and nab-paclitaxel/gemcitabine chemotherapy in advanced pancreatic cancer: An interim report. J Clin Oncol [Internet]. Feb 1, 2020 [cited March 1, 2024];38(4_suppl):716. Available at: https://doi.org/10.1200/jco.2020.38.4_suppl.716

24. Kandi V, Vadakedath S. Clinical Trials and Clinical Research: A Comprehensive Review. Cureus [Internet]. Feb 16, 2023 [cited March 10, 2024]. Available from: https://doi.org/10.7759/cureus.35077

25. Chawla SP, Chua VS, Fernandez L, Quon D, Saralou A, Blackwelder WC, Hall FL, Gordon EM. Phase I/II and Phase II Studies of Targeted Gene Delivery In Vivo: Intravenous Rexin-G for Chemotherapy-resistant Sarcoma and Osteosarcoma. Mol Ther [Internet]. Sep 2009 [cited 10 Mar 2024];17(9):1651-7. Available from: https://doi.org/10.1038/mt.2009.126

26. Goel S, Ocean AJ, Parakrama RY, Ghalib MH, Chaudhary I, Shah U, Viswanathan S, Kharkwal H, Coffey M, Maitra R. Elucidation of Pelareorep Pharmacodynamics in A Phase I Trial in Patients with KRAS-Mutated Colorectal Cancer. Mol Cancer Ther [Internet]. Mar 10, 2020 [cited Mar 10, 2024];19(5):1148-56. Disponível em: https://doi.org/10.1158/1535-7163.mct-19-1117.

27. Bradbury PA, Morris DG, Nicholas G, Tu D, Tehfe M, Goffin JR, Shepherd FA, Gregg RW, Rothenstein J, Lee C, Kuruvilla S, Keith BD, Torri V, Blais N, Hao D, Korpanty GJ, Goss G, Melosky BL, Mates M, Leighl N, Ayoub JP, Sederias J, Feilotter H, Seymour L, Laurie SA. Canadian Cancer Trials Group (CCTG) IND211: A randomized trial of pelareorep (Reolysin) in patients with previously treated advanced or metastatic non-small cell lung cancer receiving standard salvage therapy. Lung Cancer [Internet]. Jun 2018 [cited 10 Mar 2024];120:142-8. Available from: https://doi.org/10.1016/j.lungcan.2018.03.005.

28. Eriksson E, Milenova I, Wenthe J, Ståhle M, Leja-Jarblad J, Ullenhag G, Dimberg A, Moreno R, Alemany R, Loskog A. Shaping the Tumor Stroma and Sparking Immune Activation by CD40 and 4-1BB Signaling Induced by an Armed Oncolytic Virus. Clin Cancer Res [Internet]. 23 May 2017 [cited 10 Mar 2024];23(19):5846-57. Available at: https://doi.org/10.1158/1078-0432.ccr-17-0285

29. Garcia-Carbonero R, Bazan-Peregrino M, Gil-Martín M, Álvarez R, Macarulla T, Riesco-Martinez MC, Verdaguer H, Guillén-Ponce C, Farrera-Sal M, Moreno R, Mato-Berciano A, Maliandi MV, Torres-Manjon S, Costa M, del Pozo N, Martínez de Villarreal J, Real FX, Vidal N, Capella G, Alemany R, Blasi E, Blasco C, Cascalló M, Salazar R. Phase I, multicenter, open-label study of intravenous VCN-01 oncolytic adenovirus with or without nab-paclitaxel plus gemcitabine in patients with advanced solid tumors. J Immunother Cancer [Internet]. Mar 2022 [cited March 10, 2024];10(3):e003255. Available from: https://doi.org/10.1136/jitc-2021-003255

30. Freytag SO, Barton KN, Zhang Y. Efficacy of oncolytic adenovirus expressing suicide genes and

interleukin-12 in preclinical model of prostate cancer. Gene Ther [Internet]. Jul 11, 2013 [cited March 10, 2024];20(12):1131-9. Available from: https://doi.org/10.1038/gt.2013.40