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Combination of Interferons for Advanced Renal Cell Carcinoma

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1. Abstract

Introduction: A novel formulation that combines IFN alpha-2b and gamma evidenced effectivity in cancer treatment. The poor prognosis of advanced renal cancer needs new therapeutic approaches. A retrospective study was carried out evaluating the effectivity and safety of interferon's combination in patients with advanced renal cell carcinoma.

Methods: Retrospective case-control and cohort analyzes were performed, carried out to identify patients with advanced or metastatic kidney tumors treated from May 2009 to December 2021 in a Cuban healthcare center. Patients with advanced renal cell carcinoma received a combination of IFN alpha-2b/gamma. Heberon Alpha R was used as historical control. The study was approved by the Ethics Committee and informed consent was obtained for participating patients.

Results: 56 patients were included. The combination of IFNs (experimental group) and the Heberon Alpha R (historical control group) were comparable. Overall survival in stage III disease was 101.3 months with combination of IFNs versus 38.1 in Heberon Alpha R, and 70.4 months versus 30.6 months in stage IV patients. The functional capacity of patients from experimental group was higher than those from control and reached more than 75%, with favorable functional capacity at 24 months; while more than 65% of patients in the control cursed with worse capacity. No serious adverse events with proven causality occurred within the cohort of patients treated with interferon combination. The events correspond to those reported in other studies.

Conclusions: The combination of interferon's was effective and safe for patients with advanced kidney cancer.

1. Introduction

Renal cell carcinoma (RCC) has an incidence of approximately 400,000 cases per year globally [1]. It is the most aggressive of urological cancers, represents 3% of adult

tumors [2,3] and is the sixth leading cause of cancer death with 95,000 annual deaths worldwide [4]. The prognosis of RCC is poor as 30% of patients have metastatic disease at diagnosis with a 5-year survival rate of only 12% [5].

Clear cell RCC (cCRC) is the most common histological subtype and accounts for over 75% of RCCs, in comparison to non-clear cell RCC (nccCRC), which consists of 15 histological subtypes, including papillary and chromophobe histology [6]. The causes of the origin of RCC are unknown, with multiple environmental, acquired and genetic risk factors, which are more or less directly related to it. Hereditary syndromes are considered among the genetic risk factors [7].

In the past, treatment options for RCC have been very limited. Radical surgery is the only effective treatment with curative potential for localized kidney cancer. It is indicated in more advanced stages; for example, in tumors that invade the vena cava or that present minimal adenopathic disease [8,9]. After radical treatment, a variable percentage of patients may present local or systemic progression. Progression-free survival (PFS) is between 1 and 2 years [10,11]. Most kidney cancers are resistant to chemotherapy. In some patients, the combination of gemcitabine with capecitabine or fluorouracil temporarily reduces tumor size [12,13]. Radiotherapy is not effective as primary treatment, it is rarely used alone due to the damage it causes to the healthy kidney, it is only used if a patient cannot undergo surgery, and it is usually used only in areas of dissemination [14].

Target therapies that have been approved by the Food and Drug Administration (FDA) for use in metastatic RCC (mRCC) include sorafenib, bevacizumab + IFN-α, sunitinib, temsiromilus, everomilus, and pazopanib improved survival outcomes for patients with metastatic RCC.

In study R-2012/2019 – 3602-007, which included patients with progressive RCC, Sorafenib promoted a PFS of 8.6 months and overall survival (OS) of 71 months were observed [15]. A comparative study between sunitinib and pazopanib showed PFS of 8 months in both groups, and OS of 22/21 months, with notable toxicity of sunitinib [16]. The Keynote 426 and Javelin 101 studies with axitinib showed PFS at 12 and 15 months. Everolimus as second line treatment showed PFS of 4.4 and OS of 19.6 months [17] and for temsirolimus it was 5.4 months of PFS and 8.7 months OS [18].

The anti-VEGF monoclonal antibody, bevacizumab administered intravenously and combined with IFN-α applied subcutaneously, was approved for the treatment of mRCC in 2009 by the FDA, with PFS of 11.2 months and OS of 33.6 months [16]. These targeted therapies induce few complete responses in patients and have shown toxicity, without achieving notable survival benefits. Between 20% and 30% of patients with ccCRC do not benefit from kinase inhibitors, which are expensive and toxic.

More recently, the use of immune checkpoint inhibitors (ICIs) that include programmed cell death protein-1 (PD-1) inhibitors (such as nivolumab and pembrolizumab), programmed death-ligand 1 (PD-L1) inhibitors (such as atezolizumab, durvalumab, and avelumab), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors (such as ipilimumab) [19], have been widely used for treating various cancers, including RCC [20-22].

The use of ICIs nivolumab and ipilimumab is now approved for first-line treatment of intermediate and poor-risk mRCC and has demonstrated improved overall survival across multiple clinical trials [23-27] and are increasingly used as the first-line treatment for metastatic cCRC. However, the efficacy of ICI monotherapy for the treatment of solid malignant tumors is limited [28] and the combination with kinase inhibitors developed not depreciable toxicity [29].

There is an unmet clinical need for tolerable and effective approaches to the treatment of patients with advanced or mRCC. The use of combination therapy for cancer treatment is gradually increasing.

The IFNs- α and γ exert their functions through different but related signaling pathways, which include specific membrane receptors for each of these IFNs, which bind to the Janus-kinase (JAK)-activating proteins, and transcription activators and signal translators (STAT, *Signal Transducers and Activators of Transcription*), which propagate the signal towards the nucleus of the cells where the genes that respond to these two IFNs are found [30].

These both cytokines are known to mediate antineoplastic effects and contributes to cancer control by enhancement of antigen presentation, expression of IFN pathway signaling molecules, production of chemokines, inhibition of cell proliferation, induction of cell death and inhibition of angiogenesis [31-32]. The importance of IFN signaling emerged as crucial for response to chemotherapy, radiotherapy, immune checkpoint inhibitor therapy, and epigenetic drugs [33]. The accumulated evidence of the last years suggests the determinant role of IFNs in response to therapy of patients with cancer.

Since 2009, a retrospective study has been carried out at the "Arnaldo Milián Castro" Surgical Clinical Hospital in Villa Clara, Cuba, to evaluate the effectiveness and safety of the

application of a combination of interferon's in patients with renal tumors in advanced stages, without other therapeutic options available.

3. Patients And Methods

3.1 Data

Patients with advanced or metastatic kidney cancer received treatment with interferon alpha or with a combination of interferon's between 2009 and 2016 at the "Arnaldo Milián Castro" Provincial Clinical Surgical University Hospital, in Villa Clara, Cuba. Inclusion criteria were: age ≥18 years, any gender and skin color, Eastern Cooperative Oncology Group (ECOG) scale25 ≤1 diagnostic criteria, imaging evaluation, hematopoietic parameters in the normal range, at least 4 weeks after surgery and with the criteria of recovery, patients of childbearing age should use an effective contraceptive method, express written voluntariness of the patient. The exclusion criteria were the following: myocardial infarction in the last 6 months, severe or unstable angina, coronary or peripheral bypass implantation, symptomatic congestive heart failure, cerebrum-vascular accident or transient ischemic attack, pulmonary embolism. Pregnancy, puerperium or lactation, active infection, hypersensitivity to Interferon, heart, respiratory or chronic arterial failure, severe hematological or coagulation disorders, liver enzymes >5 times normal range, chronic decompensate diseases, diseases with metabolic compromise, very poor general condition. compromised, severe psychiatric disorder.

3.2 Treatment and study design

A single-center, retrospective study was conducted in eligible renal cell carcinoma patients who had received treatment with interferon alfa or the combination of interferon's. The Experimental Group (EG) received the combination of interferon's intravenously, 7 MIU of a mixture of alpha and gamma interferon's were administered subcutaneously in a volume of 5 mL twice a week, for four weeks during the induction phase. In the maintenance phase, 3.5 MIU of the mixture was administered, with the same frequency of administration. The Control Group (CG) was treated with alpha interferon, 10 MIU of subcutaneous alpha interferon were administered in a volume of 5 mL three times a week for four weeks during the induction phase. In the maintenance phase, 5 MIU were administered with the same frequency of administration.

3.3 Outcomes and assessments

OS was defined as the date of diagnosis until death from any cause or date of last seen. PFS was defined as the date from drug treatment to the date of onset of disease progression. Disease progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). At each visit, functional capacity was assessed according to the ECOG scale. Follow-up visits occurred every week for the first month and then every three months until the end of the study.

This research project was approved by the Institutional Scientific Council and the Clinical Research Ethics Committee, who evaluated it from a scientific, methodological and ethical point of view. It was determined that it complied with the Declaration of Helsinki (Ethical Principles for Medical Research in Human Beings, adopted by the World Medical Assembly, Seoul 2008) and its procedures were carried out in accordance with the provisions of the national and international codes of ethics and current legal regulations in Cuba (Norms of Good Clinical Practices, CECMED 2001), as well as in the Guide to Good Clinical Practices of the International Conference on Harmonization.

3.4 Statistical analysis

Descriptive statistics were used for the control variables, such as mean, median, minimum and maximum, percentage rate. The homogeneity of the groups was determined by comparing the control variables. For sex and histological type, the Chi-square test was used. For skin color, presence of metastases at inclusion and closure, and co morbidities present, Fisher's exact test was used. For age, tumor stage, nuclear grade, type of nephrectomy and functional capacity at the beginning of the study, the Mann-Withney test was used. Regarding functional capacity throughout the investigation, the Mann-Withney test was used. Survivorship curves were completed by means of the Kaplan-Meier methods with a log-rank test.

4. Results

132 patients diagnosed with kidney cancer were identified in the inclusion period. 76 patients were excluded, 61 of them did not meet the diagnostic criteria of presenting the disease in advanced stages and in 15 cases some exclusion criteria were presented. Fifty-six patients were eligible for analysis. In these cases, 32 received the combination of interferon's and 24 the interferon alpha. The details of the discontinuation of treatment after one year and two years are detailed in Figure 1.

After statistical analysis, it was considered that both groups were comparable at the beginning of the investigation. The demographic and baseline characteristics of both groups are shown in Table 1.

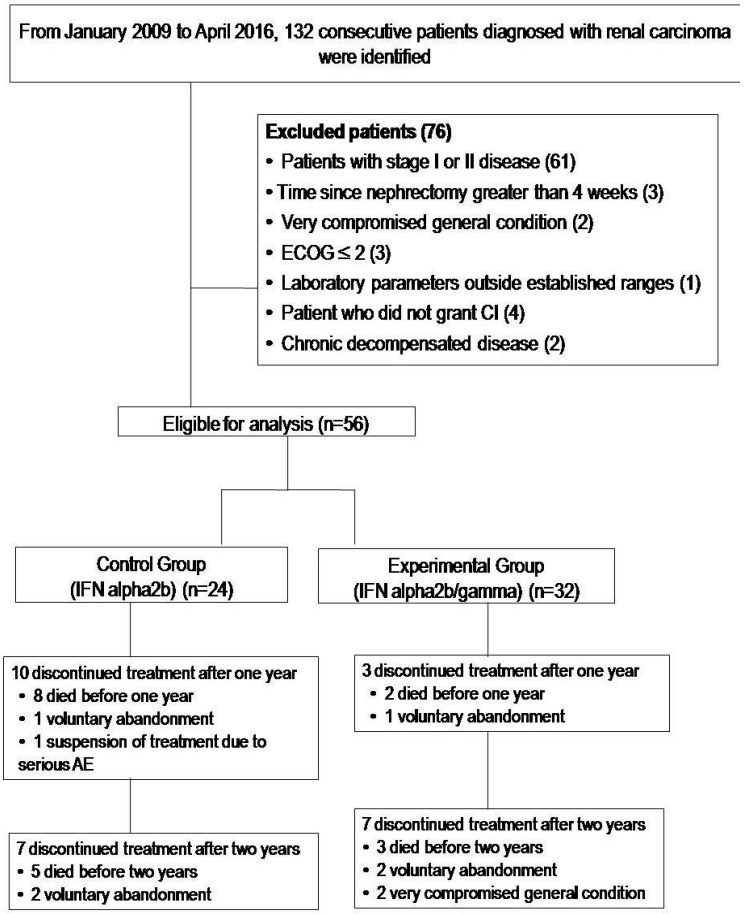

Figure 1: Flow chart showing the methods applied when identifying patients with advanced kidney cancer, to assess their survival with the combination of interferon's or with interferon alpha, as well as the continuity of treatments at one and two years after inclusion.

Both in the total sample and by groups, a predominance of males and white skin color was observed. The masculinity ratio raised a prevalence of 2.6 men for every woman, which may be related to the greater exposure of the male sex to known risk factors that favor the appearance of the disease. The average age of 57.9 in the EG and 59 years in the CG, the sexual and ethnic distribution of the patients was similar to that reported worldwide. In both groups, stage III prevailed, while stage IV was presented in 37.5 and 33.3% for EG and CG, which coincided with other authors [27, 28] who reported between 30 and 40% of metastatic patients at diagnosis. The presence of metastasis at inclusion was higher in the EG. The predominant histological type in both groups was clear cell carcinoma.

The Fuhrman nuclear grade is the most widely accepted histological grading system in CRC and is an independent prognostic factor. Although the classification and stereological measurement of the International Society of Urological Pathology has shown more reliable results in recent studies [34], given the early start date of this research, the Fuhrman graduation was used. The study found a prevalence of patients with Furhman 2 and 3 in both groups. ECOG was also described as a prognostic factor for survival in multivariate analyses, both in other cite, [35] where it was described as an independent factor for survival, and where it was related to the impact of immune status markers of the host on overall survival [36]. In this study, for the CG, 58.33% were included with an ECOG 1, while in the EG, 78.12% started treatment with ECOG 1. In no scenario did optimal functional capacity prevail.

4.1 Progression-free survival and overall survival by study group.

Three evaluations of PFS and OS were performed, at 12 and 24 months and at the end of the study, the results are shown in table 2.

The survival curves according to Kaplan Meir are shown in figure 2.

Table 1: Distribution of patients according to demographic and baseline characteristics.

		Groups		
		Exp. N=32	**Control n=24**	**P**
Gender	Male	19 (59.4%)	16 (66.7%)	0,577
	Female	13 (40.6%)	8 (33.3%)	
Skin color	White	27 (84.4%)	15 (62.5%)	0.598
	No white	5(15.6%)	9 (37.5%)	
Age	Mean	57.9	59	0.534
	Median	60.5	60.1	
	(Mín; Máx)	(41; 83)	(41; 79)	
Tumor stage	III	20 (62.5%)	16 (66.7%)	0.750
	IV	12 (37.5%)	8 (33.3%)	
Co-morbidities	Doesnotrefer	17 (53.1%)	17 (70.8%)	0.036
	One	8 (25%)	7 (29.2%)	
	Twoor more	7 (21.9%)	0	
Histological type	Clear cell	23 (71.87 %)	22 (91.66 %)	0.101
	Cromophobe	4 (12.5 %)	0	
	Solid Papillary	1 (3.12 %)	2 (6.25 %)	
	Oncocytoma	1 (3.12 %)	0	
	Undetermined	3 (9.37 %)	0	
Nuclear Grade	1	0	1 (2.4 %)	0.700
	2	12 (37.5 %)	10 (41.66 %)	
	3	12 (37.5 %)	13 (54.16 %)	
	4	5 (15.6 %)	0	
	Undetermined	3 (9.3 %)	0	
Metastasis to inclusion	Si	7 (21.9%)	1 (4.2%)	0.120
	No	25 (78.1%)	23 (95.8%)	
Type of nephrectomy	Radical	29 (90.6 %)	23 (95.83 %)	0.061
	Simple	0	1 (4.16 %)	
	Withoutsurgery	3 (9.37 %)	0	
ECOG scaleat inclusion	ECOG 0	7 (21.87 %)	8 (33.33 %)	0.342
	ECOG 1	25 (78.12 %)	14 (58.33 %)	

Table 2: Progression-free survival and overall survival.

Variable	Group	Mean	IC 95%	%	Variable	Group	Mean	IC 95%	%
Progression-free survival and overall survival by groups									
PFS-12	Exp (n=26)	64,6	53,0-76,6	89,7	**OS-12**	Exp (n=27)	70,9	58,0-83,9	93,1
	Cont (n=16)	37.7	27,4-48,7	66,7		Cont (n=21)	38,3	30,8-6,3	87,5
PFS-24	Exp (n=23)	69,9	58,8-81,0	79,3	**OS-24**	Exp (n=26)	72,8	60,0-87,5	89,7
	Cont (n=15)	39,4	28,9-49,9	62,5		Cont (n=17)	42,8	34,5-1,1	70,8
PFS Global	Exp (n=22)	81,2	66,3-96,0	75,9	**OS Global**	Exp (n=22)	135,2	111,4-159,0	75,9
	Cont (n=6)	30,7	20,1-41,3	25,0		Cont (n=6)	36,0	27,3-44,6	25,0
Progression-free survival and overall survival by groups for cases with cCRC									
PFS-12	Exp (n=20)	60,8	47,2-74,4	86,9	**OS-12**	Exp (n=21)	68,1	52,1-84,1	91,3
	Cont (n=14)	39.3	27,7-50,9	63,6		Cont (n=19)	39,5	31,1-47,9	86,3
PFS-24	Exp (n=17)	67,4	54,2-80,6	73,9	**OS-24**	Exp (n=20)	70,5	54,4-86,5	86,9
	Cont (n=13)	41,4	29,7-53,2	59,0		Cont (n=15)	44,6	35,6-53,6	68,2
PFS Global	Exp (n=22)	78,3	60,7-96,0	73,9	**OS Global**	Exp (n=17)	132,2	104,8-159,6	73,9
	Cont (n=6)	28,6	18,0-39,2	27,3		Cont (n=5)	35,6	26,5-44,7	22,7

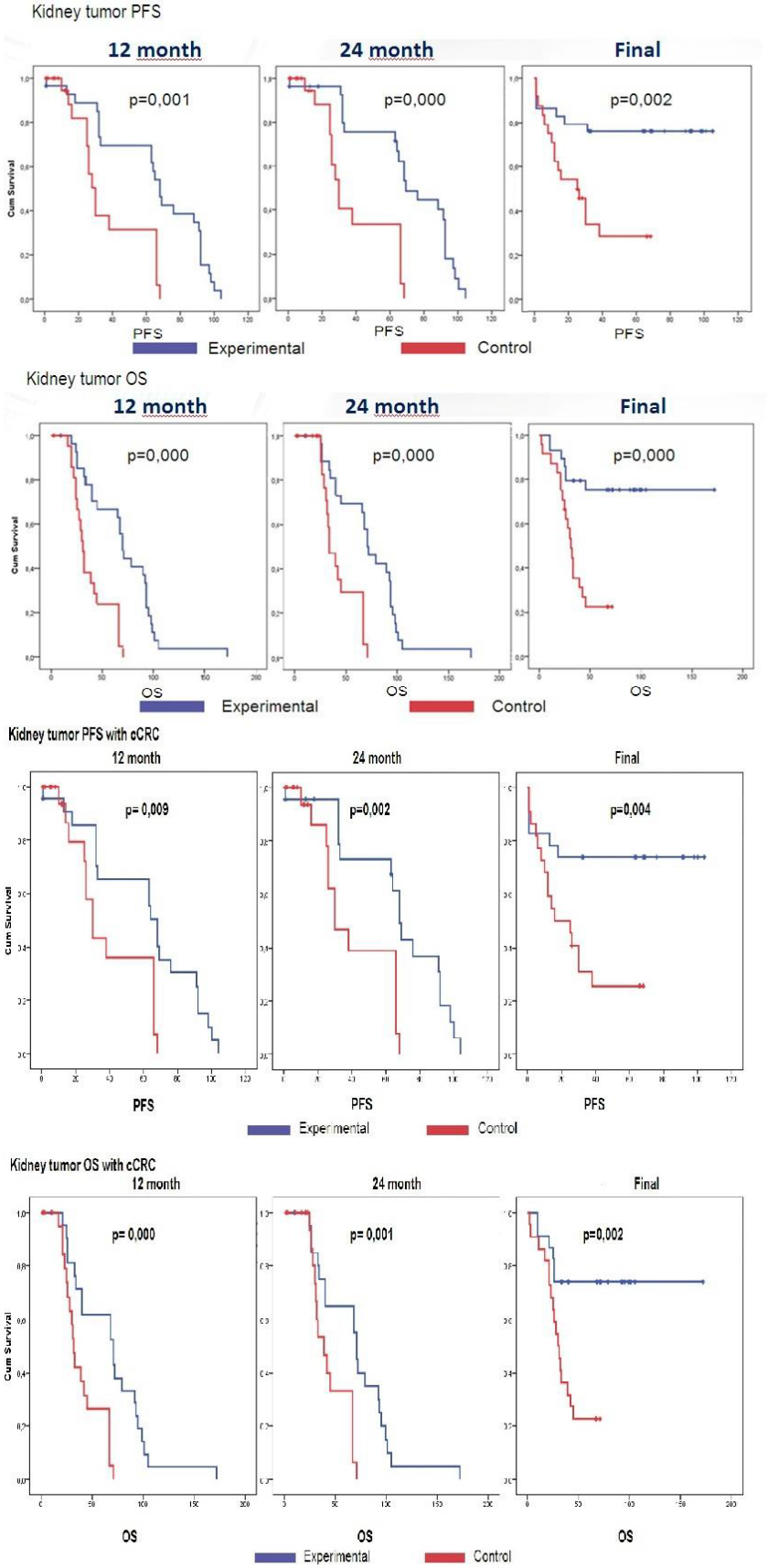

Figure 2: Kaplan Meier curves for overall survival and progression-free survival.

In the study carried out, seven patients with diagnosed metastases presented in the EG at inclusion and one case in the CG. At the end of the study, four EG patients with metastases at baseline had died, and three were still alive. In the CG, 18 cases metastasized. The differences between the groups regarding the appearance of metastases and their fatal outcome were significant according to the Monte Carlo test, with a value of p=0.000. When analyzing the number of metastases that presented by groups, the EG included four cases with a single metastasis, of which three died, with respective overall survival of two cases with 10 months and one with 26. Two patients presented two sites metastatic and both remain alive. Finally, for this group, one patient at inclusion had four sites in this condition and died, but it should be noted that he maintained an overall survival of 26 months. For the CG, the patient with a single metastasis at the beginning presented an overall survival of three months, the 17 patients who metastasized throughout the study in this group, reflected variable OS from 2 to 45 months. These results meet and double the 20% superiority expected for the combination of interferon's.

4.2 Progression-free survival and overall survival by study group for cases with cCRC.

In general, clear cell carcinoma is the most frequent; both in what is reported in the literature and in this study and is characterized by a more aggressive behavior than the others. For that reason, patients with this histology were processed individually; this subsample was made up of 23 patients treated with the combination of interferon's and 22 cases with interferon alpha, as shown in table 2 and figure 2.

4.3 Overall survival according to tumor stage and Furhman nuclear grade.

OS evaluations were performed at the end of the study based on tumor stage and Furhman nuclear grade by groups; the results are shown in table 3.

The survival curves according to Kaplan Meir are shown in figure 3.

In both analyzes the OS was higher in the EG with respect to the CG. Tumor stage evaluation yielded mean values of 101.3 months for stage III patients and 70.4 months for stage IV cases, with survival values of 95 and 50%. The estimate of OS according to nuclear grade showed mean values of 83.3 months for patients with nuclear grade with good prognosis (1 and 2) and 136.4 months for patients with nuclear grade CRC with worse prognosis (3 and 4), with values for survival of 75 and 76.4%.

4.4 Overall survival according to tumor stage by groups for cases with cCRC

Overall survival results according to stage and Furhman nuclear grade were also considered specifically for patients with a histological diagnosis of cCRC, the results are shown in table 3. The survival curves according to Kaplan Meir are shown in figure 3.

Table 3: Overall survival according to tumor stage and Furhman nuclear grade.

Variable	Group	Mean	IC 95%	Patients alive at the end	%
Overall survival according to tumor stage and Furhman nuclear grade by groups					
OS stage III	Exp (n=20)	101,3	94,1-108,4	19	95
	Cont (n=16)	38,1	27,5-48,7	4	25
OS stage IV	Exp (n=9)	70,4	23,4-117,5	6	50
	Cont (n=8)	30,6	17,2-44,0	2	25
OS nuclear grade	Exp (n=12)	83,3	62,2-104,5	9	75
1-2	Cont (n=11)	27.3	16.7-37.8	1	9.09
OS nuclear grade	Exp (n=17)	136.4	105.8-167.0	13	76.4
3-4	Cont (n=13)	42.4	31.4-53.3	5	38.4
Overall survival according to tumor stage and Furhman nuclear grade or cases with cCRC					
OS stage III, cCRC	Exp (n=15)	70,6	45,1-96,0	15	100
	Cont n=15)	38,4	27,1-49,6	4	26,6
OS stage IV, cCRC	Exp (n=8)	57,7	11,8-103,6	2	25,0
	Cont (n=7)	29,1	15,5-42,7	1	14,3
OS nuclear grade	Exp (n=11)	89,182	69,3-109,1	9	81,8
1-2, cCRC	Con (n=11)	27,273	16,7-37,81	1	9,09
OS nuclear grade	Exp (n=12)	121,500	81,04-161,97	8	66,7
3-4, cCRC	Cont (n=11)	42,545	30,45-54,64	4	36,4

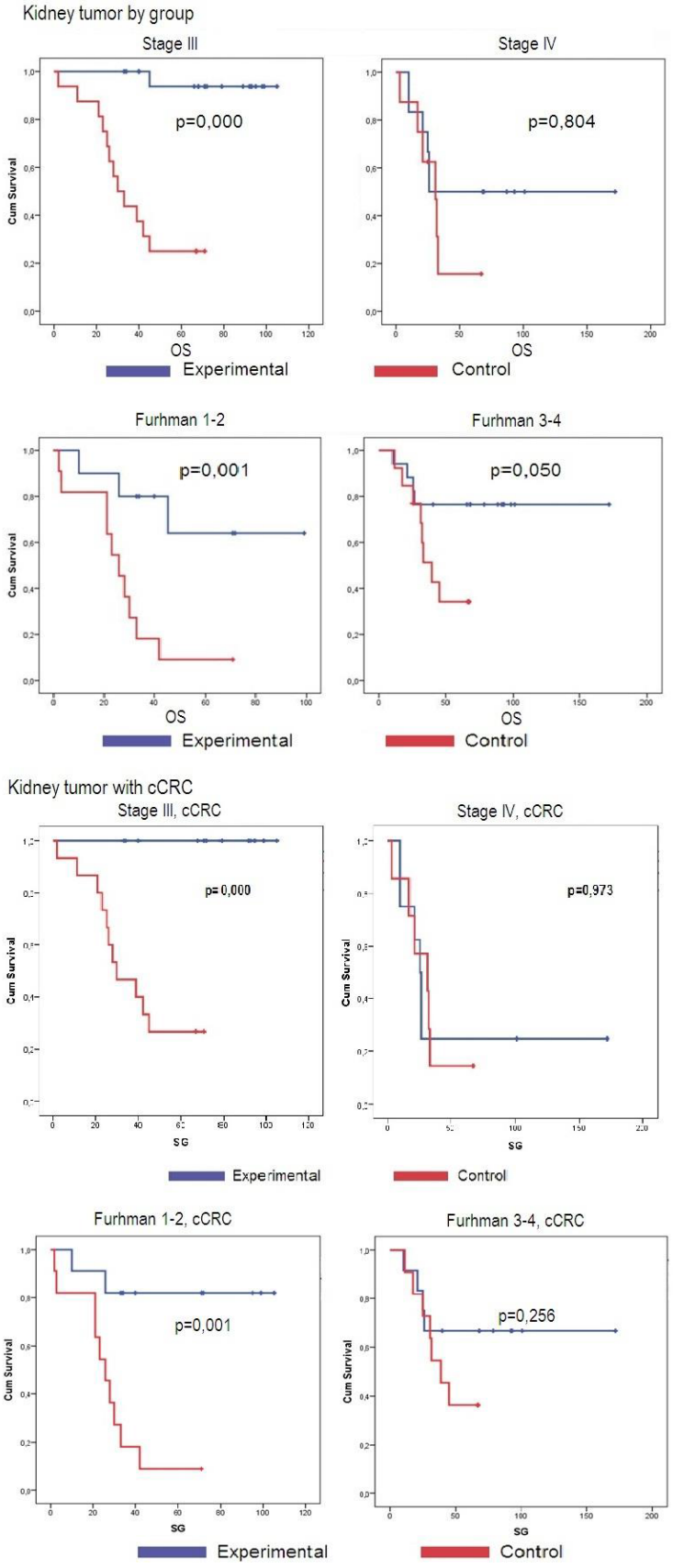

Figure 3: Kaplan Meier curves for overall survival according to tumor stage and Furhman nuclear grade.

Table 4: Demographic and tumor and clinical characteristics of patients with metastases at inclusion.

Patient	Age	Sex	Histological/ clinical diagnosis	Nuclear grade	Metastatic site	Treatment	Status at closure	OS (months)
AMC-02	67	M	12/09/2011/ccRCC	2	Regional lymph node, femur	IFNα2b/γ	21/12/2013 Deceased	26
AMC-04	58	M	18/11/2011/ccRCC	2	Iliac	IFNα2b/γ	11/12/2012 Deceased	10
AMC-06	41	F	26/03/2012/ccRCC	4	Uterus	IFNα2b/γ	22/01/2013 Deceased	10
AMC-09	66	M	15/06/2012/ccRCC	3	Kidney, liver, pancreas, lung	IFNα2b/γ	04/09/2014 Deceased	26
AMC-31	71	F	28/03/2015/Without surgery	ND	Adrenal, kidney	IFNα2b/γ	31/12/2020 Alive	68
AMC-34	63	F	06/01/2015/Without surgery	ND	Adrenal, kidney	IFNα2b/γ	31/12/2020 Alive	69
AMC-42	55	F	23/08/2005/ccRCC	3	Kidney	IFNα2b/γ	31/12/2020 Alive	172
AMC-56	70	M	01/02/2011/ccRCC	2	Lung	IFNα2b	12/05/2011 Deceased	3

Since a high number of metastatic patients were not determined at the time of inclusion, these cases were analyzed in particular. The results obtained from their demographic characteristics, about the tumor and overall survival, are shown in table 4.

4.5 Functional capacity according to the ECOG Scale.

Changes were determined with respect to the baseline value at 3, 6 and 9 months of treatment, and then after one year up to 24 months, reporting significant differences for the EG with respect to the CG in all evaluations. The results showed that despite both groups being comparable in terms of functional capacity at the time of inclusion, from the first evaluation to after three months, significant differences between the groups begin to be evident, which become more marked after the ninth month, and 81% of the patients in the EG have a favorable functional capacity, while in the CG, 70% of the patients are below ECOG 3.

4.6 Serious adverse events

When determining the percentage of patients who suffered serious adverse events, a single case was found in the EG consisting of a single confusional episode in one patient. Considering an event with a possible causal relationship with the administration of the interferon mixture that showed a reasonable temporal relationship, that did not follow a known response pattern to the drug under study and that could be caused by other factors such as the clinical state of the individual or concomitant drugs administered, the suspension of treatment in the patient in question was not considered pertinent and its application was considered safe and tolerable. In the CG, four serious adverse events were reported: nausea, vomiting, marked anorexia and irreversible weight loss, all in the same patient, which led to treatment discontinuation.

4.7 General security analysis.

520 adverse events were reported, of which 139 (26.73%) corresponded to the EG and 381 (73.27%) to the CG. The analysis of the frequency of appearance is shown in figure 4.

All adverse events were classified according to their intensity, causality relationship, measure adopted regarding treatment and result of the AE. AEs of mild or moderate intensity (Grade ≤ 3) predominated in general (99.03%), with probable or definite causal relationship (91.34%) with the application of treatment, which did not generate changes in medication (94.42%) and with recovery in most cases (83.26%). When analyzing the variables by group, a predominance of the same categories reported in the global analysis was observed, with the exception of the causal relationship, a probable predominance (60.43%) in the EG and definitive (68.76%) in the CG, whose differences were statistically significant. The differences regarding the patients recovered from the AE were significant, with 100% in the EG compared to 77.16% in the CG.

5. Discussion

The PFS and OS obtained in this study were compared with those reported in the literature in the various international

treatment schemes for advanced kidney cancer. Regarding bevacizumab, median PFS for metastatic renal tumors of 4.6 months has been proposed [37], other authors [38] reported median PFS of 11.2 and 34-month OS in the group treated with bevacizumab plus atezolizumab in a study for patients with renal cell carcinoma over expressing programmed death ligand 1 (PD-L1). Another study [39] reported a median PFS and OS of 20.7 and 28.3 months, respectively, for patients who received bevacizumab and pembrolizumab as first-line treatment. In relapsed patients, the PFS of the combination was 9.9 months and the OS was 17.9.

Regarding kinase inhibitors, axitinib has been used in numerous investigations for CRC, a retrospective study [40] where it was used as third or fourth line of treatment in patients with advanced kidney cancer, raised a mean PFS of 6.27 months and OS of 19.2 months. For metastatic patients treated with axitinib [41], 5.7 months of PFS were reported, with 15.4 OS. A study that combined axitinib and pembrolizumab versus sunitinib [42] resulted in a PFS of 15.1 vs 11.1 months. A comparative study of cabozantinib versus everolimus in three groups stratified by age [43] established PFS of 7.4, 8.1 and 9.4 months for cabozantinib and 3.8, 3.9 and 4.4 months for everolimus; regarding OS, it defined 21.4, 18, and 18.4 months for cabozantinib and 17.1, 18, and 14 months for everolimus. A study [44] that treated low- and intermediate-risk patients with metastatic renal cell carcinoma with pazopanib obtained 9.5 and 4.3 months OS and PFS, respectively. Another kinase inhibitor is sorafenib [45], compared with tibozanib, a vascular endothelial growth receptor inhibitor, PFS of 3.9 and 5.6 months, respectively, was obtained in patients with metastatic CRC, who received the drugs as third or fourth line treatment; regarding OS, 16.4 months were determined for tivozanib and 19.7 months for sorafenib.

Everolimus and temsirolimus are inhibitors of the mammalian target of rapamycin (mTORC1) complex, a serine-threonine kinase that plays a central role in the regulation of cell growth, proliferation and survival. Nivolumab is a human immunoglobulin (IgG4) monoclonal antibody that binds to the PD-1 receptor; blocks its interaction with PD-L1 and PD-L2, as well as release of the PD-mediated response pathway inhibition -1, including the anti-tumor immune response, the blockade of PD-1 activity produces a decrease in tumor growth. Treatment outcome as second-line everolimus therapy in metastatic RCC patients after failure of kinase [46] inhibitors was PFS of 3.8 and OS of 16.8 months. A comparative study with nivolumab or everolimus as third-line therapy [47] showed PFS of 4.2 and 4.5 and OS of 25.8 and 19.7 months, respectively. A study with temsirolimus [48] to treat patients with inoperable renal tumors resulted in PFS of 4.5 months and another study [49] described 14.9 months of PFS in patients with metastatic renal cell carcinoma treated with nivolumab.

The results obtained in this study by combining interferon's are considered superior.

The marked incidence of serious adverse events in the worldwide therapeutic options for kidney tumors was characteristic of the literature reviewed for this purpose. Regarding bevacizumab [37] reported grade 3 and higher toxicities in 16 patients (57%) who received bevacizumab compared to 19 (61%) who received bevacizumab plus a monoclonal antibody. Other studies [38] described that patients who received atezolizumab plus bevacizumab compared to sunitinib had fewer grade 3-4 adverse events: 182 cases for 40% of 451 in the first group against 240 events for 54% of 446 in the second group, however, these figures are very high compared to the results obtained here. Other authors [39] described 45% of grade 3 or 4 adverse events, at least possibly related to pembrolizumab or bevacizumab treatments, the most common grade 3 related to treatment were hypertension, proteinuria, adrenal insufficiency and pain / headaches, and two patients with grade 4 toxicity (hyponatremia and duodenal ulcer).

Regarding kinase inhibitors, axitinib referred by other cite [40] caused grade 3 and higher toxicity in 31% of patients and the dose had to be reduced in 5 (22%) cases and the drug had to be suspended in 3 patients (13%). Other authors [41] reported grade 3 or 4 treatment-related AEs in 79% and 26% of patients. Eleven patients had to discontinue the study due to toxicity. The study showed that the combination of pembrolizumab + axitinib [42] produced grade ≥3 adverse reactions in 75.8% of patients (vs. 70.6% in the sunitinib group), while the grade ≥3 adverse reactions were less frequent in the nivolumab + ipilimumab group compared to the sunitinib group; treatment discontinuation rates for toxicity were 10.7% for pembrolizumab + axitinib (both drugs), 22% for ipilimumab + nivolumab, and were comparable with sunitinib in both studies (13.9% and 12%).

In studies comparing cabozantinib with everolimus [43] reported that the toxicities of both generally increased with age, with grade III/IV AEs occurring in 8.0% in any treatment group of the three subgroups of ages. For pazopanib [44], reported hypertension as the most common grade 3/4 treatment-related AEs, reported in 4.7% of patients. Another kinase inhibitor, sorafenib, was compared with tibozanib, [45] treatment-related serious AEs occurred in 19 (11%) patients on tivozanib and 17 (10%) patients on sorafenib.

Other authors [46] reported on the safety of everolimus treatment that the most common related AEs ≥ grade 3 were anemia (12.7%), hyperglycemia (6.3%), interstitial lung disease (3.2%), increased blood triglycerides (3.2%) and hypertriglyceridemia (3.2%) and five fatal AEs were reported during treatment. In a comparative study with nivolumab or everolimus [47] as third-line therapy, in all treated patients, the overall incidence of treatment-related AEs was 21.4%, in the nivolumab group and 36 .8% in the everolimus group (grade 3 or 4). Other studies [48] showed the safety results with temsirolimus, serious treatment-related AEs occurred in 226 (22.6%) patients, and other [49] described the safety of nivolumab treatment with four cases (10%) of severe AEs, which also led to treatment discontinuation.

The results for the EG obtained in this study were considered superior.

The results of the overall security scan generally coincided with those reported in the literature for interferon combinations. The study [50] in various scenarios of cancer treatment with HeberFERON, a new formulation of interferon's with improved pharmacodynamics, reported one hundred and ten different AEs in 259 patients (80%). The most frequent events (≥10%) were fever, chills, asthenia, arthralgia, headache, anorexia, myalgia, perilesional edema and erythema, and nausea. Most of the AEs were mild (89.6%) and 12.0% moderate. The treatment approach adopted for most events did not involve dose changes (96.8%) and most AEs disappeared (87.9%). 78% of the events were classified as very likely to be related and 11.4% as likely to be related to the proposed formulation. The investigation [51] on basal cell carcinoma of the face treated with HeberFERON showed that patients presented pain and burning at the injection site, in addition to a predominance of fever, headache, and edema and perilesional erythema. Other authors [52] reported that palpebral erythema and pain at the injection site were the most frequent ocular adverse events (95.0 and 70.0%) and occurred in 95% of the patients treated in their study about safety of HeberFERONin patients with palpebral basal carcinoma. Systemic adverse events (fever, arthralgia and headache) prevailed in 100% of cases, with mild intensity.

Regarding interferon alpha, the study was one of the most comprehensive and collected the safety of the product during 28 years of application in Cuba [53], after application in 5 806 patients. AEs were reported in 4 864 subjects (84%) and 18 234 reports of adverse events were collected, with 211 different types of manifestations, where 185 (88%) were detected by physical examination, while 26 (12%) corresponded to alterations in normal levels of hematology, biochemistry and endocrine parameters evaluated by the clinical laboratory. The main AEs corresponded to the flu-like syndrome, given by fever, headache, myalgia, chills, arthralgia and asthenia, reported by more than a thousand patients (≥ 20%). Among the hematological events, the most frequent was anemia in 15%.

6. Conclusions

The clinical benefit of the administration of the combination of interferon's for patients with advanced renal cancer was demonstrated with the completion of this study. The superiority in PFS and OS obtained for the combination is significant and even superior to standardized therapies in the world and approved by drug regulatory agencies. The safety of the product in relation to the adverse events presented was also evidenced, considering that the drugs approved for this pathology have been the subject of multiple investigations to determine their therapeutic safety.

This study had some limitations; firstly, the use of a historical control instead of a concurrent control may have increased the risk of observation bias on the part of the investigators. Second, the possibility of under-registration of adverse events cannot be excluded, although this risk was mitigated by requesting and explicitly collecting the events from the patients. Finally, the findings of the present study may not be representative of the CRC treatment experience, due to the fact that it is not a large sample, however, since a strict surveillance of all cases was carried out in the study, the results they are very generalizable to normal medical practice.

7. Conflict of Interest

There is no conflict of interest.

8. Contribution of the Authors

María Margarita Ríos Cabrera MSc: conceptualization, formal analysis, research, methodology and writing.

Iraldo Bello Rivero PhD: formal analysis, methodology and writing.

Javier Cruz Rodríguez PhD: formal analysis, methodology and writing.

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