cancers

MDPI

Systematic review and meta-analysis

Metformin as adjuvant treatment in hematological malignancies.

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Simple Summary: There are more than ten hematological malignancies, which together occupy third place in the general classification of cancer, behind lung and breast malignancies; however, leukemias, myelomas and lymphomas are the most frequent. Several studies have shown a higher incidence of solid tumors and hematological malignancies in patients with type 2 diabetes mellitus (T2DM). Among the different types of cancers analyzed, a beneficial effect on oncologic pathology has been additionally found with the use of metformin, an oral hypoglycemic widely used in the treatment of T2DM, suggesting that metformin could become an anticancer agent in the future. In the present investigation, the effectiveness of the use of metformin as an adjuvant treatment in hematological malignancies will be analyzed.

Abstract: Objective: To evaluate the effectiveness of the use of metformin as adjuvant treatment in patients diagnosed with hematological malignancies. Methods: a literature search was performed in Medline, Scopus, Embase, Lilacs, Google Scholar and grey literature databases, without language restriction. Heterogeneity among the included studies was assessed using the Q statistic and the RI coefficient. A fixed and random effects model was used to summarize the outcome of complete remission and event-free survival in patients who had used metformin as adjuvant treatment in their oncologic pathology. Results: nine studies were found, of which 6 were taken to meta-analysis. The results showed metformin as a risk factor for complete remission in clinical trials with a statistically non-significant RR, for retrospective studies a statistically significant OR, in terms of survival no difference was found between the two groups. Conclusions: In patients diagnosed with acute lymphoblastic leukemia, diffuse large B-cell lymphoma and follicular lymphoma, metformin was shown to be a risk factor for complete remissions, however, with non-significant results.

Keywords: Metformin, Antineoplastic Agents, Hematologic Neoplasms, Leukemia, Lymphoma, Myeloma

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1. Introduction

Metformin is a drug of the biguanide family widely used in the treatment of T2DM since the last century. In adults, treatment with metformin is generally initiated with doses of 500 mg -850 mg twice daily with an increase of 500 mg every week or 850 mg every two weeks being able to reach a maximum daily dose of 2550 mg [1], being the most widely used oral antihyperglycemic in the world due to its low rate of adverse effects, its low cost in the market and the wide clinical experience that support it [2]. Its antidiabetic effects are mainly based on the inhibition of gluconeogenesis and the improvement of insulin resistance in peripheral tissues, where it improves glucose utilization, lowering glycemia and exerting better control over insulin hypersecretion typical in T2DM. Its adverse effects are limited, the most frequent being gastrointestinal intolerance; it can cause lactic acidosis in only 0.00003% of patients [3].

However, the usefulness of metformin as an antidiabetic is not the only one demonstrated, in recent years it has been shown that this drug slows the growth of certain types of cancer, which has been the subject of intense research, all these effects occur by a complex mechanism of action that to this day is not completely known. Two possible mechanisms of metformin as an antineoplastic have been proposed, the first is the inhibition of oxidative respiration acting on the mitochondrial complex I of the mitochondrial respiratory chain which causes a decrease in the production of adenosine triphosphate (ATP), resulting in an increase in the concentration of adenosine diphosphate (ADP), which is transformed into adenosine monophosphate (AMP), with subsequent stimulation of Adenine Monophosphate Activated Protein Kinase (AMPK), producing activation of reactive nitrogen radicals, which stimulate protein kinase C that phosphorylates the tumor suppressor protein kinase LKB1, resulting in inhibition of AKT/mTOR pathway signaling and ultimately suppression of cell proliferation [4].

The second proposed mechanism is based on reduced concentrations of insulin and insulin-like tissue growth factor-1 (IGF-1), a hormone that promotes the growth of many cell types, whereby its inhibition results in decreased growth promotion and mutagenesis [4].

Hematological neoplasms, as a whole, occupy the third place in the general classification of cancer, behind lung and breast malignancies. Although more than ten blood cancers have been identified, lymphomas, leukemias and myelomas are the most frequent [5]. AMPK/mTOR signaling pathway is involved in the pathogenesis of many of these blood malignancies, consequently, metformin, through activation of AMPK, can suppress cancer cell proliferation [6], published in vitro studies confirm the beneficial effects of metformin, and indicate that AMPK is an attractive target for the treatment of acute and chronic leukemia, Vakana Et al [7] , demonstrated that AMPK activators such as metformin, are potent in suppressing leukemic precursors of chronic myeloid leukemia and acute myeloid leukemia, including cells with BCR-ABL mutation (mutation formed by the combination of two genes, which appear in patients with certain types of leukemia). The study by Shi et al [8], reported that metformin induced cell growth suppression in both B-cell and T-cell lymphomas through negative control of the AMPK/mTOR pathway, and in multiple myeloma elevated expression in this pathway has also been observed so that AMPK activators could be used as a treatment [6].

Taking into account the above, metformin represents a new perspective in the therapy of hematological cancer, so the present systematic review aims to evaluate the effectiveness of the use of metformin as an adjuvant treatment in hematological neoplasms, based on the premise of authors who indicate that metformin is an excellent antidiabetic drug that continues to amaze researchers and clinicians for its recently analyzed antitumor effects. Many epidemiological studies show evidence in favor of metformin in terms of improving

the prognosis of patients with different types of malignant tumors and it can even prevent the appearance of tumors such as prostate, lung, head and neck, breast, pancreatic, colorectal, ovarian and liver cancers [9]. Obviously, it will never replace targeted therapies, but it can be a great low-cost adjuvant in the treatment of this type of oncological patients.

2. Materials and Methods

Type and design of study

A systematic review was performed in accordance with the recommendations of the PRISMA consensus for reporting systematic reviews and meta-analyses.

Methodology

A literature search was conducted until November 1, 2022, in databases such as Medline, Scopus, Embase and Lilacs, academic Google, non-indexed literature, gray literature database such as open Grey and also used the snowball search strategy in generic internet search engines, of studies conducted, which evaluated the effectiveness of the use of metformin as adjuvant treatment in different types of hematological malignancies, using the following search terms MESH: Metformin, Hematologic Neoplasms, Leukemia, Leukemia, Myeloid, Leukemia, Lymphoid Multiple Myeloma, Lymphoma, Lymphoma, Non-Hodgkin Lymphoma, Hodgkin, Lymphoma, B cell Lymphoma, T cell anticancer drug, Antineoplastic Agents. The following combinations were used for the search: (Metformin) AND (Hematologic Neoplasms), (Metformin), AND (Leukemia OR, Lymphoma, OR Myeloma), (Metformin) AND (Lymphoma, Non-Hodgkin OR Lymphoma, Hodgkin) AND (Antineoplastic Agents, OR anticancer drug), (Metformin) AND (Lymphoma, B cell OR Lymphoma, T cell) AND (Antineoplastic Agents, OR anticancer drug), (Metformin) AND (Leukemia Myeloid), OR Leukemia Lymphoid) AND (Antineoplastic Agents, OR anticancer drug) y (Metformin) AND (Multiple Myeloma) AND (Antineoplastic Agents, OR anticancer drug).

Selection of studies

The study designs included were: case-control, cohort, cross-sectional analytical cohort, controlled clinical trials, systematic reviews with or without meta-analysis, without language restriction; case report studies, case series, narrative reviews and animal studies were excluded.

The records obtained were evaluated by a reviewer through RAYYAN tool to collect and examine articles, duplicate studies obtained in the search were eliminated, then a selection of studies was made according to the title and abstract, the articles selected after this phase were taken to full review independently by two reviewers selecting those that met eligibility criteria, the quality of the studies was evaluated through two scales OXFORD for clinical trials and STROBE for observational studies

Risk of bias

The risk of bias was assessed through the Cochrane Collaboration Tool, this tool addresses six specific domains: Selection bias, conduct, detection, attrition, reporting and other bias, Within each item, two parts were included, the first part included the description of how it happened in the study and the second part included the assignment of a rating in relation to the risk of bias for that item, assigning each item a rating of 'Low risk' of bias, 'High risk' or 'Unclear risk' of bias, with high risk indicating low item quality, low risk indicating

high item quality, and unclear risk of bias indicating that limited information restricted the correct judgment to identify low or high item quality.

Statistical Analysis

A meta-analysis was performed using the EPIDAT 3.1 program, where the results of the studies were divided into two groups: Prospective studies and retrospective studies. The heterogeneity test was evaluated using the Q statistic considering statistical significance a value less than 0.05, and the I2 considering significant values greater than 25%. The results of each study were summarized by means of a Forest plot with RR or OR effect measure as appropriate to the study, using a fixed and random effects model to determine the overall effect. Publication bias was evaluated using the Funnel plot and the Begg and Egger test considering a statistically significant value of less than 0.05.

3. Results

A total of 2,184 records were obtained in the described databases, finding: Medline, 317 articles; Lilacs, 435; Base, 1342; Scopus, 89; and open Grey, 1 record. Additionally, records were searched in other sources such as academic Google where 7500 records were found, from these 148 duplicate articles were eliminated, later the articles were chosen by title, excluding 9342 articles, 194 articles found in the databases were read for the abstract. of data and in academic Google, later inclusion and exclusion criteria were applied to carry out a complete reading of 16 articles, of which 7 articles were eliminated with a final of 9 records, of which 6 were taken to meta-analysis (figure 1).

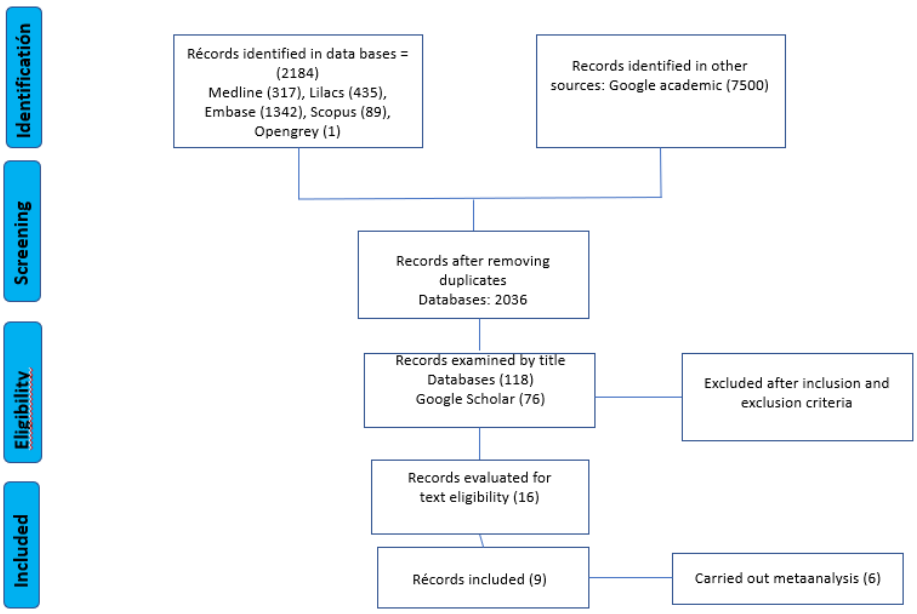

Figure 1. PRISMA Flowchart, Figure made by the author.

Study characteristics

Table 1 shows the characteristics of the included studies. The selected studies were conducted in Mexico [10,11,12,17], USA [13,14,15], Australia [16], China [18], hematological neoplasms included were acute lymphoblastic leukemia (ALL), diffuse large b-cell

lymphoma (DLBCL) and follicular lymphoma, the studies were developed between 2010 and 2019.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis

First Author Year/Country	Study design	No. Participants	Subjects	Years	Intervention dose	Control	Primary outcome	Reference
Ramos 2014 México	clinical trial	93	Patients LLA	16-65 years	Metformin 850 mg three times daily + chemotherapy regimen HGMLAL07/09	Chemotherapy regimen HGMLAL07/09	Complete remission 81.3% vs 70% in favor of the non-metformin arm, Early relapses (first year of treatment) 47.9% vs 25% in favor of the non-metformin group.	10
Ramos 2015 México	Cases and controls	151	Patients LLA	16-66 years	Metformin 850 mg three times daily + chemotherapy regimen HGMLAL07/09	Chemotherapy regimen HGMLAL07/09	Favorable Steroid Response (RFE) (59.1% vs. 26.2% in favor of the metformin group (OR; 0.24 95% CI 0.11 - 0.51) and Complete Remission (CR) rates 81.3% vs. 57.9%, in favor of the metformin group (OR 0.30 95% CI 0.13-0.72).	11
Ramos 2018 México	clinical trial	123	Patients LLA	17-79 years	Metformin 850 mg three times daily + chemotherapy regimen HGMLAL07/09	Chemotherapy regimen HGMLAL07/09	Remisión completa 72.4 % vs 10.6% y Recaídas tempranas: riesgo de recaída (RR: 2,58 (1,24-5,37), p = 0,006) en comparación con aquellos que recibieron en conjunto metformina (RR: 0,38 (0,18-0,80) 95% IC)..	12
Wynn 2019 USA	Cohort	38	Type 2 diabetic patients diagnosed with lymphoma	64.1 - 73.3 years	diabetic patients who were taking metformin 6 months prior to cancer diagnosis and continued to take metformin at least 1 year after cancer diagnosis. metformin at least 1 year after diagnosis.	Diabetic patients with lymphoma who had not taken metformin	Recurrence 44.4% vs 35% in favor of the metformin group (p =0.552) New tumors 16.7 vs 10% in favor of the metformin group (p=0.653)	13
Wang 2019 USA	Cohort	1764	Patients with LCBG and follicular lymphoma		Metformin 500 mg daily or 1000 mg twice daily	Diabetic patients with lymphoma who had not taken metformin	Overall and event-free survival in LCGB DM/metformin (HR = 1.05; 95% CI 0.59-1.89) or DM/No metformin (HR = 1.41, 95% CI 0.88-2, 26) for follicular lymphoma with patients without DM/without metformin, there was no association of DM/metformin (HR = 116; 95% CI 071–189) or DM/No metformin (HR = 1.16, 95% CI 066 -204).	14
Alkhatib 2016 USA	Cases and controls	48	Diabetic patients diagnosed with LCBG	Over 18 years	Diabetic patients taking metformin	Diabetic patients with lymphoma who had not taken metformin	Complete remission 92% vs 54% in favor of the metformin group OR 18.6 (95% CI 2.15–161; p =.0018) in patients with LCGB....	15
Koo 2010	Cohort	213	Patients diagnosed with LCBG	15.5-87.2 years	Metformin + rituximab-based	Rituximab-based chemotherapy	Global response rate and complete remission (74.2 vs.	16

Australia					chemotherapy immunotherapy	immunotherapy .	78.6%; p 0.587), in patients with LCBG. Overall survival and event-free survival without significant differences p=0.141 in the treatment groups	
Ramos 2018 México	clinical trial	102	Patients diagnosed with LLA with expression of the ABCB1 gene	18-61 years	Metformin 850 mg three times daily + chemotherapy regimen HGMLAL07/09	Chemotherapy regimen HGMLAL07/09	Overall Survival 83.3% vs 26.6% in favor of the metformin user group (p=0.025) In the group of metformin users, the drug acted as a protective factor against treatment failure (odds ratio [OR] 0.07; 95% confidence interval [CI]: 0.0037-1.53) and early relapse (OR 0.05, 95% CI 0.0028-1.153).	17
Xing 2018 China	clinical trial	245	Type 2 diabetic patients diagnosed with lymphoma who had achieved complete remission after 6 cycles of R-CHOP	19-79 years	Metformin 1000 mg twice a day	Patients without metformin	SG significantly better than those who did not receive metformin maintenance, especially for diabetic patients. Patients older than 60 years, elevated LDH, or an International Prognostic Index (IPI) score ≥2 benefited from metformin maintenance.	18

LLA Acute lymphoblastic leukemia LCGB: Diffuse large B-cell lymphoma, RC complete remission, RFE: favorable response to steroids, SG overall survival, SLE disease free survival. (Table made by the author)

Table 2. Risk of bias

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias
Ramos 2014	Low risk Sequence generation + Allocation concealment +	unclear risk Blinding (unknown)	Unclear risk Blinding of evaluators (not known)	Low risk	Low risk
Ramos 2015	Low risk Sequence generation + Allocation concealment +	unclear risk Blinding (unknown)	Unclear risk Blinding of evaluators (not known)	Low risk	Low risk
Ramos 2018	Low risk Sequence generation + Allocation concealment +	unclear risk Blinding (unknown)	Unclear risk Blinding of evaluators (not known)	Low risk	Low risk
Wynn 2019	Low risk Sequence generation + Allocation concealment +	Low risk	Low risk	Low risk	Low risk
Wang 2019	Low risk Sequence generation + Allocation concealment +	Unclear risk	Unclear risk	Low risk	Low risk

Alkhatib 2016	Low risk Sequence generation + Allocation concealment +	Low risk	Low risk	Riesgo poco claro	Low risk
Koo 2010	Low risk Sequence generation + Allocation concealment +	unclear risk	Unclear risk	Low risk	Low risk
Ramos 2018	Low risk Sequence generation + Allocation concealment +	unclear risk	Unclear risk	Low risk	Low risk
Xing 2018	Low risk Sequence generation + Allocation concealment +	unclear risk	Unclear risk	Low risk	Low risk

Table produced by the author: Cochrane collaboration tool for risk of bias

Prospective Studies

Seven prospective studies were included: 4 clinical trials and 3 cohort studies, where the following outcomes were evaluated: complete remission of the disease, which was defined if the patient had less than 5% blasts in the bone marrow and recovery of neutrophil and platelet values, overall survival, defined from the date of diagnosis to the date of death or last follow-up, and event-free survival was defined as the time from diagnosis to progression or relapse of the disease.

The registry of Ramos, 2014 [10], which included 93 patients, diagnosed with de Novo Acute Lymphoblastic Leukemia (ALL) evidenced higher complete remission in the non-metformin group compared to the metformin group (81.3 vs 70%), in terms of early relapses within the first year were higher in the non-metformin group (47.9% vs 25%), while overall and disease-free survival had no significant differences in terms of type of treatment

The study of Ramos, 2018 [12] clinical trial, which included 123 patients with ALL , 72.4% integrated complete remission, the percentage of therapeutic failures was 28.3% being higher in the chemotherapy alone group, regarding the type of treatment, those patients who were only administered chemotherapy alone showed a higher risk of relapse (RR: 2.582 (1.240-5.378), p = 0.006) compared to those who received metformin together (RR: 0.387 (0.185-0.806) 95% CI), overall survival was also higher in patients who received treatment with metformin (p = 0.009).

Another clinical trial found was Ramos, 2018 [17] a study of 102 patients evaluating the impact of metformin in LLA patients with ABCB1 gene expression and determine its impact on overall survival. In these patients, increased survival was observed in the metformin user group 83.3%, compared to the non-metformin user group 26.6%, In the metformin user group, metformin is evidenced as a protective factor for therapeutic failure and early relapse (OR 0. 07, 95 % CI 0.003-1.53 and OR 0.05, 95 % CI 0.0028-1.15), and the last clinical trial included was Xing, 2018 [18] a phase II clinical trial with 245

patients evaluating the effect of metformin as maintenance in patients diagnosed with LCBG and follicular lymphoma in patients who had achieved complete remission study conducted between January 2013 to July 2017 where it was concluded that patients in the metformin arm had a longer survival with those without metformin.

The study by Wang, 2019 [14] was an observational cohort study that included 869 patients with newly diagnosed diffuse large B-cell lymphoma (LCBG) and 895 patients with follicular lymphoma, patients were divided into 3 groups those without Diabetes Mellitus (DM) and using metformin, those with DM and using metformin, and those without DM and not using Metformin, event-free survival and disease relapse or unplanned retreatment after initial management or death from any cause were evaluated. Patients with LCBG without DM/without metformin, there was no association of DM/metformin (HR = 1.05; 95% CI 0.59-1.89) or DM/No metformin (HR = 1.41, 95% CI 0.88-2.26) for follicular lymphoma with patients without DM/no metformin, there was no association of DM/metformin (HR = 116; 95% CI 071-189) or DM/No metformin (HR = 1.16, 95% CI 066-204).

Finally the last two studies found were Wynn, 2019 [13] study of 38 patients with diabetes mellitus with a diagnosis of lymphoma, long term survival was significantly longer in the metformin group than in the non-metformin group in lymphoma (5.89 vs. 1.29 years, $P < 0.001$), There was no significant difference in recurrence or occurrence of new malignancies for lymphoma ($P = 0$, 552 and $P = 0.653$), the last study included was KOO, 2010 [16] a study of 213 patients with a diagnosis of LCBG who had received rituximab-based chemotherapy where it was concluded that there was no significant difference in complete remission in the group of patients who did and did not receive metformin (74. 2 vs. 78.6%; p 0.587) there was no significant difference in overall survival for patients receiving and not receiving metformin (p 0.141), and for metformin-free survival events (p 0.574).

Retrospective Studies

We included 2 retrospective studies, 2 case-control study Ramos, 2015 [11] and Alkhatib, 2016 [15], The first study Ramos 2015 [11] was a study conducted in patients diagnosed with ALL, included 151 patients where complete remission was observed higher in the metformin group 81.3% vs 57.9%, (OR 0. 30 95% CI 0.13-0.72), the second case-control study was the study of Alkhatib,2016 [15] was a study of 48 patients diagnosed with DLBCL where complete remission was achieved in 92% of patients with metformin vs 54% non-metformin OR 18.6 (95 % CI 2.15-161; p =.0018).

Meta-analysis

Among the studies found, only six were taken to meta-analysis with the aim of evaluating complete remission and event-free survival.

Image 1 Complete remission in clinical trials. Comparison of metformin use with chemotherapy vs. standard chemotherapy.

RESULTADOS INDIVIDUALES Y COMBINADOS

Estudio	Año	n	RR	IC(95,0%)		Pesos(%) E. fijos	E. aleat.
Ramos	2014	93	0,8300	0,6096	1,1300	30,8746	46,7076
Ramos	2018	123	1,3100	1,0659	1,6100	69,1254	53,2924
Efectos fijos		216	1,1378	0,9586	1,3506		
Efectos aleatorios		216	1,0585	0,6775	1,6539		

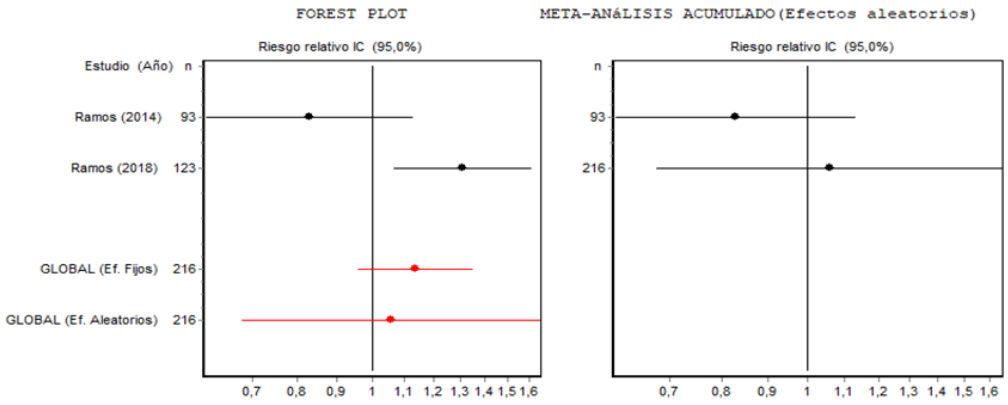

Image 1 shows the results of the meta-analysis of two clinical trials in patients with LLA, with a total of 216 participants, intervention group (81) and control group (135), using both fixed and random effects model, the analysis of the results allow us to conclude that patients with a diagnosis of acute lymphoblastic leukemia treated with metformin 850 mg every 8 hours with chemotherapy have 1, 13 times (fixed effects) and 1.05 times (random effects) the risk of presenting complete remission compared to patients with hematological malignancies who were treated with chemotherapy alone, however with a confidence interval that is not statistically significant.

Image 2 Complete remission in case-control studies. Comparison of metformin use with chemotherapy vs. standard chemotherapy.

RESULTADOS INDIVIDUALES Y COMBINADOS

Estudio	Año	n	OR	IC(95,0%)		Pesos(%) E. fijos	E. aleat.
Ramos	2015	151	3,2600	1,3820	7,6900	86,3473	66,8311
Alkhatib	2016	88	18,6000	2,1488	161,0000	13,6527	33,1689
Efectos fijos		239	4,1350	1,8627	9,1792		
Efectos aleatorios		239	5,8086	1,1646	28,9717		

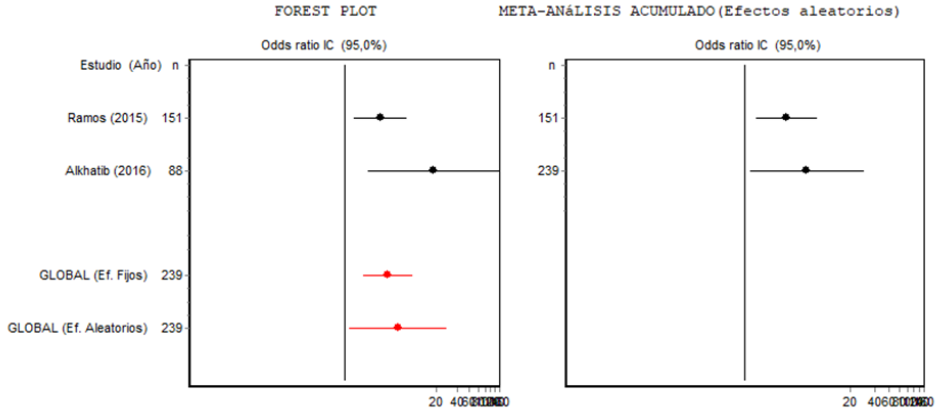

Image 2 shows the results of the meta-analysis of 2 case-control studies with a total number of participants of 239, 151 patients with ALL and 88 with LCBG, in the case group (68) and in the control group (171), using both fixed and random effects models, with either method of analysis the results allow us to conclude that patients who presented complete remission are 4.13 times (fixed effects) and 5.80 times (random effects) more likely to have been treated with metformin + chemotherapy compared to those who did not present complete remission, with a statistically significant 95% confidence interval.

Image 3 Event-free survival prospective studies. Comparison of metformin use with chemotherapy vs. standard chemotherapy

RESULTADOS INDIVIDUALES Y COMBINADOS

Estudio	Año	n	OR	IC(95,0%)		Pesos(%) E. fijos	E. aleat.
KOO	2010	213	0,7200	0,3988	1,3000	15,0987	26,6981
WANG	2019	893	1,7800	1,2474	2,5400	41,6982	36,5172
WANG	2019	869	1,7700	1,2482	2,5100	43,2031	36,7847
Efectos fijos		1975	1,5489	1,2311	1,9486		
Efectos aleatorios		1975	1,3950	0,8717	2,2325		

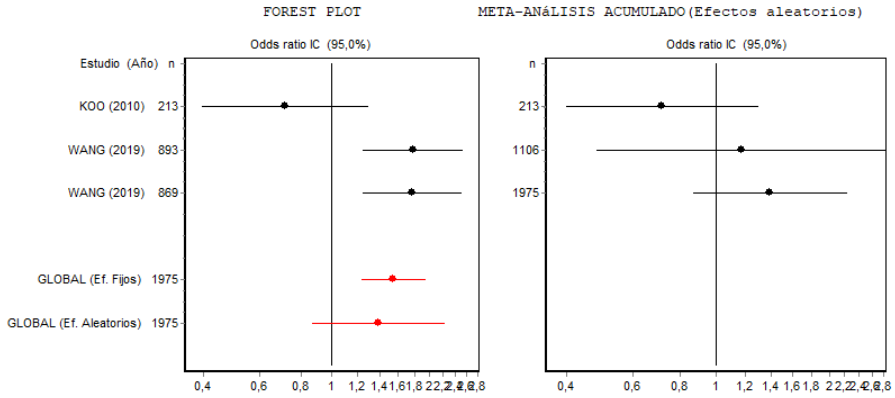

Image 3 shows the results of the event-free survival meta-analysis of two prospective studies, with a total of 1975 participants, diagnosed with follicular lymphoma (893) and CBCL (1082), in the metformin group (116) and in the control group (1859), using both the fixed-effect and random-effects models, with an HR of 1.54 (fixed effects) and an HR of 1.39 (random effects), with either method of analysis the results allow us to conclude that there is no difference in survival in either treatment group, with a statistically non-significant confidence interval

Publication bias

When evaluating Begg's test (1.0), none of the studies showed publication bias.

4. Discussion

Although there are more than a dozen blood cancers, in the analysis of clinical studies performed, it was only possible to evaluate the use of this drug in three hematological cancers: acute lymphoblastic leukemia LLA, diffuse large B-cell lymphoma LDCBG and follicular lymphoma, complete remission was considered to a number of blasts in bone marrow less than 5% and a count of leukocytes and platelets in blood as normal, these results were meta-analyzed in two groups, the first was conducted with two clinical trials that evaluated patients diagnosed with LLA who were managed with chemotherapy

protocol of HGMLAL07/09 , In the second group, 2 case-control studies were analyzed in patients diagnosed with LLA and LDCBG, where an association in favor of the metformin group was found to achieve complete remission, which was statistically significant, although with a wide interval, which could be explained by the sample size used.

In addition, survival in follicular lymphoma and LDCBG was analyzed in the studies by Wang 2019 [14] and KOO 2010 [16], which evaluated event-free survival defined as the time from diagnosis to disease progression or relapse, where a HR was observed with no difference in survival between the two treatment groups, however, with a statistically non-significant confidence interval.

Another outcome evaluated in the clinical studies was relapse, defined as patients who had been in complete remission and who presented an increase in the number of blasts greater than 5%. In the studies with patients diagnosed with LLA, metformin could be evidenced as a protective factor for relapse, as was the case in the study by Ramos, 2018 [12] where a RR of 0.38 (95% CI 0.18-0.80) was evidenced, as well as Ramos 2014 [10] where the group of patients who received chemotherapy without metformin had a higher percentage of relapses compared to the group with metformin (47.9 and 25%).

Although in several in vitro studies metformin has been shown to be a promising drug in hematological cancers due to its mechanism of action on AMPK and the AKT/mTOR signaling pathway [7,8], the low number of clinical trials and observational studies generates uncertainty in the results which are not conclusive, Furthermore, it is important to note that the high heterogeneity among the studies that evaluated the effect of metformin affected the study data, the included studies varied in the characteristics of the study population such as patients with diabetes/non-diabetes, types of cancer, sample size, duration and dose of metformin treatment.

The risk of bias was generally considered low; however, some items were rated as unclear, following the recommendations of the consensus for reporting systematic reviews and meta-analyses PRISMA [19].

5. Conclusions

In patients diagnosed with acute lymphoblastic leukemia, diffuse large B-cell lymphoma and follicular lymphoma, metformin was shown to be a risk factor for complete remissions with a statistically non-significant RR for the prospective studies evaluated and a statistically significant OR for the retrospective studies, in terms of event-free survival in follicular lymphoma and diffuse large B-cell lymphoma there was no evidence of difference between the two treatment groups.

Although in recent years metformin has been suggested as a new drug in different types of cancer, the results of this review and meta-analysis are not conclusive; the design of more studies, such as randomized clinical trials with adequate sample sizes, is required to make a definitive conclusion.

Conflicts of Interest: No conflicts of interest to declare

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