Malignant Pleural Mesothelioma Chemotherapy Treatment: Systematic Review

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Tratamento Quimioterápico do Mesotelioma Pleural Maligno: Revisão Sistemática

Tratamiento Quimioterápico del Mesotelioma Pleural Maligno: Revisión Sistemática

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Abstract

Introduction: Malignant pleural mesothelioma is a rare, aggressive cancer that is expected to increase in incidence by 2030. The best ways to treat this neoplasm are still under discussion. **Objective:** To synthesize the evidence of efficacy and safety of the different first-line chemotherapy regimens available for the treatment of malignant pleural mesothelioma. **Method:** The LILACS, MEDLINE, Scopus, Cochrane Controlled Trials Register and Web of Science bibliographic databases were used. Studies were sought in the grey literature. Eligibility criteria included randomized phase II or III trials of chemotherapy-naive patients with pleural mesothelioma who underwent any therapeutic regimen, compared to other chemotherapeutic regimens or active symptom control, and presenting overall survival, progression free survival, tumor response and toxicity as outcomes. All steps were performed independently by two reviewers. The review protocol was recorded in the International Prospective Register of Systematic Reviews (PROSPERO 2014: CRD42014014388). **Results:** Thirteen studies involving fourteen therapeutic regimens were included. The only chemotherapy regimen that presented superior to the comparator with statistical significance in the three efficacy outcomes was cisplatin + pemetrexed. Cisplatin + pemetrexed and cisplatin + gemcitabine presented more grades 3 and 4 toxicity cases. **Conclusion:** There is good evidence to recommend combinations of platinum and antifolate derivatives as a first-choice option in the chemotherapeutic treatment of pleural mesothelioma. Further clinical studies are needed to support decisions to incorporate antifolates in the routine treatment of this neoplasm in Brazil.

Key words: Mesothelioma; Drug Therapy; Lung Neoplasms.

Resumo

Introdução: O mesotelioma pleural maligno é um câncer raro, agressivo e que apresenta expectativa de aumento na incidência até 2030. As melhores formas de tratar essa neoplasia continuam em debate. **Objetivo:** Sintetizar as evidências de eficácia e segurança dos esquemas quimioterápicos de primeira linha disponíveis para o tratamento do mesotelioma pleural maligno. **Método:** Foram utilizadas as bases bibliográficas LILACS, MEDLINE, Scopus, *Cochrane Controlled Trials Register* e *Web of Science*. Buscaram-se estudos na literatura cinzenta. Os critérios de elegibilidade incluíram ensaios randomizados de fases II ou III, de pacientes com mesotelioma pleural virgem de tratamento quimioterápico, submetidos a qualquer regime terapêutico, tendo como controle outros esquemas quimioterápicos ou controle ativo de sintomas, e apresentando tempo de sobrevida global, tempo livre de progressão, resposta tumoral e toxicidade como desfechos. Todas as etapas foram realizadas por dois revisores, de forma independente. O protocolo da revisão foi registrado no *International Prospective Register of Systematic Reviews* (PROSPERO 2014: CRD42014014388). **Resultados:** Treze estudos envolvendo 14 esquemas terapêuticos foram incluídos. O único esquema quimioterápico que se apresentou superior ao comparado com significância estatística nos três desfechos de eficácia foi cisplatina + pemetrexede. Cisplatina + pemetrexede e cisplatina + gemcitabina apresentaram mais casos de toxicidade graus 3 e 4. **Conclusão:** Existem boas evidências para recomendar combinações de derivado de platina e antifolato como opção de primeira escolha no tratamento quimioterápico do mesotelioma pleural. Mais estudos clínicos são necessários para embasar decisões de incorporação dos antifolatos no tratamento rotineiro dessa neoplasia no Brasil.

Palavras-chave: Mesotelioma; Tratamento Farmacológico; Neoplasias Pulmonares.

Resumen

Introducción: El mesotelioma pleural maligno es un cáncer raro, agresivo y que presenta expectativa de aumento en la incidencia hasta 2030. **Objetivo:** Sintetizar las evidencias de eficacia y seguridad de los diferentes esquemas quimioterápicos de primera línea disponibles para el tratamiento del mesotelioma pleural maligno. **Método:** Se utilizaron las bases bibliográficas LILACS, MEDLINE, Scopus, *Cochrane Controlled Trials Register y Web of Science*. Se buscó estudios en la literatura gris. Los criterios de elegibilidad incluyeron ensayos aleatorizados de fase II o III, de pacientes con mesotelioma pleural vírgenes de tratamiento quimioterápico, sometidos a cualquier régimen terapéutico, teniendo como control otros esquemas quimioterápicos o control activo de síntomas, y presentando tiempo de supervivencia global, tiempo libre de progresión, respuesta tumoral y toxicidad como resultados. Todas las etapas fueron realizadas por dos revisores, de forma independiente. El protocolo de la revisión se registró en el *International Prospective Register of Systematic Reviews* (PROSPERO 2014: CRD42014014388). **Resultados:** Se incluyeron trece estudios de catorce esquemas terapéuticos. El único esquema quimioterápico que se presentó superior al comparador con significancia estadística en los tres resultados de eficacia fue cisplatino + pemetrexede. Cisplatino + pemetrexed y cisplatino + gemcitabina presentaron más casos de toxicidad grados 3 y 4. **Conclusion:** Existen buenas evidencias para recomendar combinaciones de derivado de platino y antifolato como opción de primera elección en el tratamiento quimioterápico del mesotelioma pleural. Más estudios clínicos son necesarios para basar decisiones de incorporación de los antifolatos en el tratamiento rutinario de esa neoplasia en Brasil.

Palabras clave: Mesotelioma; Tratamiento Farmacológico; Neoplasias Pulmonares.

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INTRODUCTION

Malignant pleural mesothelioma is an occupational cancer originated in the mesothelial and submesothelial cells of the pleura. It is a rare neoplasm and, sometimes, hard to differentiate from lung adenocarcinoma. Its main symptoms are thoracic pain, dyspnea and weight loss that happen progressively, usually of late diagnosis and in advanced staging of the disease[1]. Independently of its histologic type, survival after diagnoses is slim[2].

More than 80% of the cases of malignant pleural mesothelioma are related to the previous professional exposure to asbestos and there is a dose-response with areas of incidence higher in the industrial facilities that use this mineral intensely[3,4]. Despite the prohibition of asbestos in several Brazilian states, the incidence of malignant pleural mesothelioma is growing. Because of the extended period of latency of these tumors, not until 2030 its drop is anticipated [5].

Brazil is the world biggest producer, consumer and exporter of asbestos and approximately 300 thousand workers were exposed to the product in 2010[6]. Studies about asbestos exposure cancer-related are scarce in the country because of the diagnosis difficulties and sub-reporting of cases, mainly. It were registered 2,308 deaths by mesotheliomas from 2000 to 2012 in the country, but it is estimated that this number is underestimated, being anticipated that the mortality by this cancer continues to grow for the next 15 to 20 years[6].

The diagnosis and therapeutic approach of this neoplasm remains difficult and complex[2]. Its treatment is multimodal consisting of surgery, radiotherapy and chemotherapy. Patients eligible for curative treatment have an average survival of 13 to 47 months and those submitted to palliative treatment, barely reach 8 to 12 months. Non-epithelial histological type, high *performance status*, advanced staging of the disease, older than 49 years, male, thoracic pain, weight loss, low level of hemoglobin, thrombocytosis, leukocytosis and high level of lactate dehydrogenase are associated to poor prognosis [2].

The majority of the patients have unresectable or inoperable disease at the diagnosis because of age or presence of clinical comorbidities, being usually treated with systemic chemotherapy to prolong the survival and improve the quality of life[7]. There are controversies about the best therapeutic regimens for the diseases with some cases becoming resistant, occasionally.

There is not still in the country a clinical trial or therapeutic guideline about the disease and its rarity hampers the collection of samples with the required statistical power to justify a clinical trial of high quality. In addition, the expectation that the number of mesotheliomas from the use of asbestos happens to increase along the time, makes it extremely relevant to provide the existing information about the efficacy and safety of the therapeutic regimens utilized in the drug treatment of the malignant pleural mesothelioma.

This systematic review summarized the evidences about the efficacy and safety of the first line regimens available for the treatment of the malignant pleural mesothelioma.

METHOD

The protocol of the review was registered at the *International Prospective Register of Systematic Reviews* (PROSPERO 2014:CRD42014014388). The review considered only Phase II or III randomized clinical trials of chemotherapy treatment in naive-treatment patients with malignant pleural mesothelioma.

It were utilized the bibliographic databases MEDLINE (via *Pubmed*), LILACS, Scopus, *Cochrane Controlled Trials Register* and *Web of Science*. It was also searched the base of clinical trials *Clinical Trials*. The searches were conducted in March 2019, without definition of the initial period to recover the references.

Search strategies adapted to the researched base and designed with the assistance of a librarian included the search of descriptors or disease-related words in the text ["mesothelioma", "pleural neoplasms", "pleural cancer"], type of intervention ["drug therapy", "antineoplastic agents", "chemothera-py"] and type of study ["randomized controlled trial", "controlled clinical trial", "random allocation]. The complete strategy of the trial can be obtained with the authors.

The search strategy for the base Medline (via Pubmed) was the following: (((eothelioma[mh] OR Mesothelioma[ti]) AND (Pleural Neoplasms[mh] OR Pleural[ti]) AND (drug therapy[sh] OR drug therapy[tiab] OR drug*[tiab] OR drug therapy[tw] OR "antineoplastic agents"[All Fields] OR "antineoplastic agents"[mh] OR antineoplastic agents[tw] OR chemotherap*[tiab])) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh]))).

It were examined the bibliographic references of the clinical trials included in this systematic review, in the reviews and clinical guidelines mentioned in this work and in Annals of Congresses recovered from the searched bibliographic bases, and in unidentified articles.

The inclusion criteria were: (a) randomized clinical trials with comparison groups where chemotherapy as exclusive treatment or as part of a multimodal treatment (in combination with surgery or radiotherapy); (b) studies utilizing chemotherapy regimen or placebo as group control; (c) trials presenting as outcome: time of global survival, progression-free survival, tumor response and toxicity (adverse events); (d) works published in English, Portuguese, Spanish and French. Studies with participants with other neoplasms or other types of mesothelioma when permitted the extraction in separate of the data of the participants with malignant pleural mesothelioma were included as well. Comparative clinical trials without group control or investigating second line chemotherapy treatment, editorials, letters or revisions were excluded.

The citations were stored and handled in the references manager software (*EndNote*). Duplicates of references were eliminated. The bibliographic references corresponding to Annals of Scientific Congresses were investigated in search for studies that addressed the eligibility criteria.

The selection of studies was made by two reviewers and the discrepancies were resolved by consensus. It consisted of two phases: analysis of titles and abstracts and reading of complete texts. The extraction form was elaborated with the following information: a) information about the authors: year of publication, intervention, comparison and outcomes reported; b) characteristics of the study: number of participants, histological type, staging of the disease, extension and access to the tumor, number of research sites and countries involved, average time of diagnosis, average time of follow up and loss to follow up; c) characteristics of the participants: age, gender, race, *performance status* and duration of the symptoms; d) treatment with drugs: finality of the chemotherapy, multimodal treatment, previous treatment and concomitant therapy; e) outcomes: the definitions of each outcome according to the authors of the studies were extracted and compared, in addition to the results of the outcomes of interest and toxicity of the therapeutic regimens.

The following outcomes were investigated: global survival time defined as the time passed since the entry of the patient in the study until death; progression-free survival corresponding to the interval between the entry of the participant in the study until the progression of the disease or death; tumor response means the rate of the participants who presented some response to the treatment, which is measured in two ways: objective response rate (ORR), which is the rate of participants who presented total or partial response to the treatment and disease control rate (DCR), which is the sum of ORR and of the participants who stabilized the disease. The toxicity was represented by the occurrence of adverse events associated to different chemotherapy regimens, being considered the presence of toxicity of any degree and, specifically, of scores 3 (severe), 4 (with risk of death or disability) and 5 (death associated to adverse event).

The evaluation of the methodological quality of the studies available as a complete text took into consideration the process of randomization, secrecy of the assignment, blinding, analysis of intent-to-treat and losses during the studies, factors considered more relevant by Cochrane in the evaluation of risk of bias in randomized controlled clinical trials[8]. Two independent reviewers were utilized and possible differences were resolved by consensus.

The average results of the outcomes and respective confidence intervals of 95% of the therapeutic regimens were registered as found in the manuscripts. It was plotted a *forest plot* for the global survival time in the *software Stata* version 12.0, utilizing the standard average differences to express the effect of the treatments, with confidence intervals of 95%. The standard average difference was obtained by the rate of the average difference of the results of the outcome among the groups and the standard deviation of these results among the participants of the study. When sufficient data to calculate the standard deviation of the outcomes means were insufficient, it was adopted the mean of the standard deviations of the other studies present in the same analysis[8]. Data of adverse events were reported as absolute number and relative frequency as encountered in the clinical trials.

The great heterogeneity of the results of the studies, resulting from the difference of therapeutic regimens and groups control hampered the meta-analysis.

RESULTS

It were identified 4,136 studies in the bases searched and 32 by cross reference search and in other sources. After the elimination of 1,144 duplicates, the titles and abstracts were investigated, being excluded 2,996. Of the 28 studies evaluated as complete text, 13 met the eligibility criteria and were included in the review[9-21]. Ten were published as complete articles [9-16,19,21] and three as abstracts of congress[17,18,20]. Figure 1 summarizes the results of the phases of selection and motives for exclusion.

Table 1 presents the main characteristics of the studies and participants. The number of participants in the studies varied from 25 to 448 (median 87) with only four trials including more than 100 patients. The

medians of age varied from 56 to 72 years. In the 11 studies that brought information about histological type of the malignant pleural mesothelioma, the epithelial type was predominant [9-13,15,16,18-21]. The proportion of patients with *performance status* 0-1 was higher than 80% in eight studies[9-12,15-17,19]. In 11 studies, only participants without surgical indication were eligible[9-15,17-20]. In the seven studies that informed the time of follow up, this time varied from 10 to 45 months[9,11-13,15,16,19]. The studies involved 14 different therapeutic regimens, the more frequent were the regimens that combined cisplatin associated to pemetrexed and carboplatine associated to pemetrexed, with or without the presence of another antineoplastic.

The evaluation of the methodological quality of the complete articles is shown in Figure 2. Overall, the quality of these studies was poor. Only five detailed the process of randomization[11-13,15,16] and only two mentioned the secrecy in the assignment of participants [11,16]. Only one study was double-blind[21]. The flow of participants and the losses were described clearly in eight studies[10-13,15,16,19,21]. The same eight studies were those who analyzed the results per intent-to-treat.

The therapeutic regimens and the results of the outcomes investigated are presented in Table 2. The therapeutic regimens that stood out with objective response rate over 30% were carboplatine + pemetrexed; cisplatin + gemcitabine; cisplatin + pemetrexed + CBP501; cisplatin + pemetrexed + axitinib, cisplatin + pemetrexed + bevacizumab, cisplatin + pemetrexed + nintedanib and cisplatin + pemetrexed + cediranib. The combination of carboplatine and pemetrexed reached objective response of nearly 80%.

The DCR corresponding to the sum of the participants with objective response and those where the disease was stabilized by chemotherapy was higher than 80% for the therapeutic regimens cisplatin associated to gemcitabine and carboplatine associated to pemetrexed.

The therapeutic regimens vinorelbine and those that associated the use of cisplatin with gemcitabine, of cisplatin with pemetrexed; of cisplatin, pemetrexed and axitinib; of cisplatin, pemetrexed and bevacizumab; cisplatin, pemetrexed and nintedanib; cisplatin, pemetrexed and cediranib; and derivative of platin, pemetrexed and galinpepimut-S presented median of progress-free survival bigger than six months. As for global survival time, the regimens based in the association of cisplatin + gemcitabine, cisplatin + pemetrexed, cisplatin + pemetrexed + axitinib, cisplatin + pemetrexed and bevacizumab, cisplatin + pemetrexed + nintedanib and derivative of platin + pemetrexed + galinpepimut-S showed survivals above 16 months.

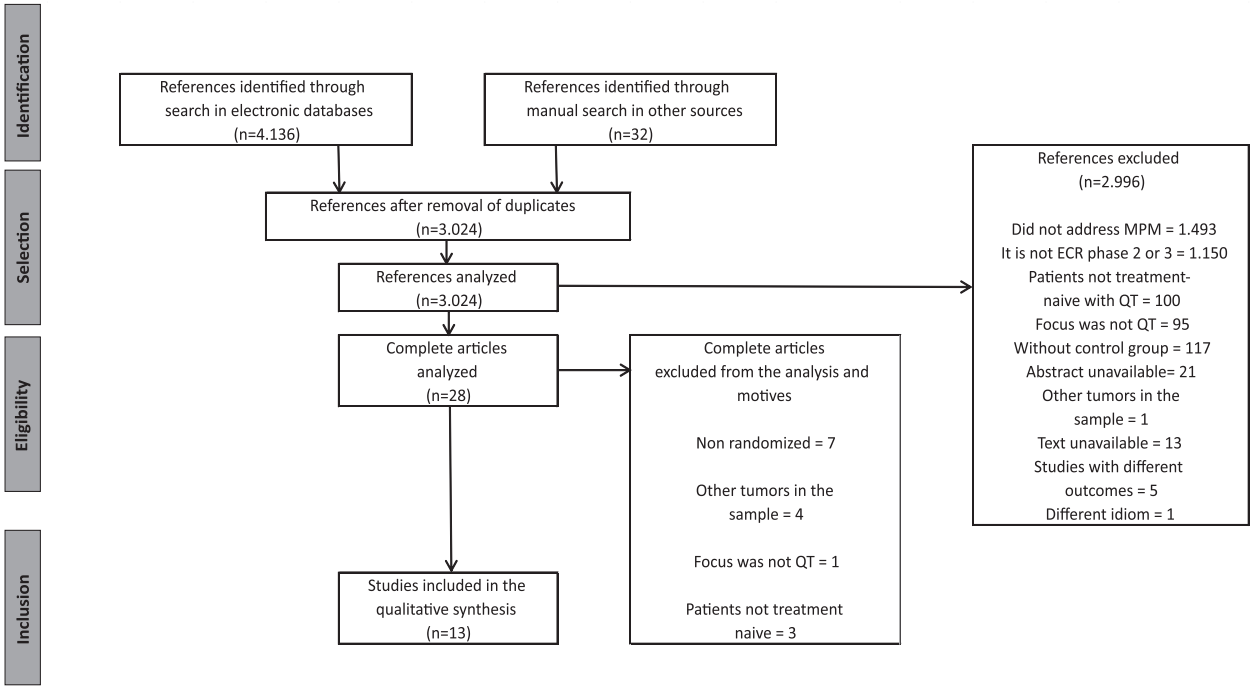

Figure 1. Flowchart of the phases of selection of the studies about chemotherapy treatment of malignant pleural mesothelioma

Captions: ECR – Randomized Clinical Trial; MPM – Malignant Pleural Mesothelioma, QT – Chemotherapy.

Table 1. Characteristics of the studies and participants included in the systematic review

Author, year	Period of the study	Time of follow up (months)	Number of patients	Median of age in years (range)	Intervention	Control
White et al., 2000	1994-1997	—	25	56 (28-72)	Cisplatin + etoposide	Carboplatine
Vogelzang et al.,2003	1999-2001	10.0	448	61 (19-85)	Cisplatin + pemetrexed	Cisplatin
van Meerbeeck et al.,2005	2000-2004	24	250	58 (19-80)	Cisplatin + raltitrexed	Cisplatin
Muers et al.,2008	2001-2006	36.4	409	65 (46-85)	Supportive care + cisplatin + mitomycin + vinblastine or supportive care + vinorelbine†	Supportive care
Millenson et al., 2010	2005-2007	—	32	71 (53-80)	Gemcitabine + pemetrexed	Carboplatine + pemetrexed
Habib et al., 2013	2008-2011	18 (6-30)	40	57 (28-74)	Cisplatin + gemcitabine	Carboplatine + pemetrexed
Krug et al., 2014	2008-2011	—	65	65 (35-84)	Cisplatin + pemetrexed + CBP501	Cisplatin + pemetrexed
Zaleman et al., 2016	2008-2014	39.4 (25.5-54.8)	448	65.7 (61.3-70.2)	Cisplatin + pemetrexed + bevacizumab	Cisplatin + pemetrexed
Buikhuisen et al., 2016	2009-2012	45	32	61 (35-75)	Cisplatin + pemetrexed +axitinib	Cisplatin + pemetrexed
Tsao et al., 2018	2011-2018	—	92	72	Cisplatin + pemetrexed + cediranib	Cisplatin + pemetrexed
Zauderer et al., 2017	2011-2015	—	46	68 (34-84)	Derivado de platin + pemetrexed + galinpepimut-S	Platin derivative + pemetrexed
Grosso et al., 2017	2013-2017	29.0 (26.9-33.1)	87	67 (39-80)	Cisplatin + pemetrexed + nintedanib	Cisplatin + pemetrexed
Kovac et al., 2017	2017*	—	96	63	Cisplatin + gemcitabine	Cisplatin + pemetrexed

Note: † — In the study of Muers11, 136 patients were submitted to treatment with supportive care + vinorelbine and 137 to supportive care + mitomycin + vimblastin + cisplatin.

Figure 2. Synthesis of the evaluation of the quality of the studies included in the systematic review

Caption: +: Realizado(a); – : Não realizado(a); ? : Não está claro.

Table 2. Measures of outcomes of the studies included, according to chemotherapy regimens for treatment of pleural malignant mesothelioma

Regimen	Author, year	ORR % (CI 95%)	CDR % (CI 95%)	PFS (months) (IC 95%)	GST (months) (IC 95%)
Vinorelbine	Muers et al., 2008	16%	75%	6.2	9.5 (7.5-12.1)
Cisplatin + raltitrexed	van Meerbeeck et al., 2005	23.6% (15.7-31.6)	76%	5.3 (4.6-6.6)	11.4 (10.1-15)
Cisplatin + gemcitabine	Habib et al., 2013	47.6%	90.5%	—	—*
	Kovac et al., 2017	50%	—	8.6	18.6
Cisplatin + pemetrexed	Vogelzang et al., 2003	41.3% (34.8-48.1)	—	5.7	12.1 (10.0-14.4)
Cisplatin + etoposídio	White et al., 2000	8%	39%	—	4.4
Gemcitabine + pemetrexed	Millenson et al., 2010	0% (0-20.6)‡	46%	3.3 (1.6-5.2)	6.0 (3.9-14.0)
Carboplatin + pemetrexed	Habib et al., 2013	78.9%	84.2%	—	—**
	Millenson et al., 2010	18.8% (5.4-41.7)‡	94%	4.1 (1.7-6.6)	13.0 (5.6-21.9)
Cisplatin + pemetrexed + CBP501	Krug et al., 2014	31% (17.0-47.6)	69% (52.4-83)	5.1 (3.9-6.5)	13.3 (9.2-16.3)
Cisplatin + pemetrexed + axitinib	Buikhuisen et al., 2016	36%	43%	5.8 (4.6-24)	18.9
Cisplatin + pemetrexed + bevacizumab	Zaleman et al., 2016	47%	74%	9.2 (8.5-10.5)	18.8 (15.9-22.6)
Cisplatin + pemetrexed + nintedanib	Grosso et al., 2017	56.8%	—	9.4 (6.7-11.2)	18.3 (15.2-28.8)
Cisplatin + pemetrexed + cediranib	Tsao et al., 2018	53.0%	—	6.9	10
Derivative of platine + pemetrexed + galinpepimut-S	Zauderer et al., 2017	—	—	7.4 (2.8-14.6)	22.8 (9.1-37.6)
Cisplatin + mitomycin + vinblastine	Muers et al., 2008	10%	72%	5.1	7.7 (6.1-7.9)

Caption: CI 95% – Confidence Interval of 95%; ORR – Objective response rate consists in total or partial response to chemotherapy; DCR – Disease control rate consists in ORR and those who had the disease stabilized; PFS – progression free-survival, in months; GST – Global survival time.

Notes: — *Does not have time median of the survival time, only that 41% of the 21 patients submitted to cisplatin + gemcitabine regimen were alive at 18 months of follow up; —** Does not bring median of survival time, only that 57.8% of the 19 patients submitted to carboplatin + pemetrexed regimen were alive at 18 months of follow up; ‡ – Confidence interval evaluated in the study was 90%.

Cisplatin associated to pemetrexed was the only therapeutic regimen that presented statistically significant standard average difference in terms of global survival time (Figure 3).

There was a report of death associated to adverse events (score 5) in the studies of Krug et al.[10], with chemotherapy regimen associating cisplatin, pemetrexed and CBP501 (2.5% of the patients); Vogelzang et al.[13] e Grosso et al.[19],

Therapeutic Regimens[Ref]	Intervention			Control			Standard medium difference (CI 95%)
	n	Med	SD	n	Med	SD	
Vinorelbine[11]	136	9.5	13.7	136	7.6	11.0	0.15 (-0.09-0.39)
C + etoposide[14]	13	4.4	16.6*	12	5.1	12.7*	-0.05 (-0.83-0.74)
C + mitomicina + vinblastina[11]	137	7.7	11.0	136	7.6	11.0	0.01 (-0.23-0.25)
C + raltitrexede[12]	126	11.4	14.0	124	8.8	8.5	0.22 (-0.02-0.47)
C + P[13]	222	12.1	16.7	222	9.3	11.0	0.20 (0.01-0.38)
Carboplatine + P[17]	16	13	15.3	13	6	8.4	0.55 (-0.20-1.30)
Gemcitabine + P[17]	13	6	8.4	16	13	15.3	-0.55 (-1.30-0.20)
C + P + CBP501[10]	40	13.3	11.1	23	12.8	11.1	0.05 (-0.47-0.56)
C + P + axitinib[15]	25	18.9	16.6*	11	18.5	12.7*	0.03 (-0.68-0.73)
C + gemcitabine	45	18.6	16.6*	51	20.6	12.7*	-0.14 (-0.54-0.26)
C + P + nintedanib[18]	44	18.3	22.4	43	14.2	14	0.22 (-0.20-0.64)
C + P + cediranib	46	10	14.4	46	8.5	14.4	0.10 (-0.30-0.51)
Platinum + P + galinpepimut-S[21]	20	22.8	30.4	21	18.3	19.6	0.18 (-0.44-0.79)
C + P + bevacizumabe[16]	223	18.8	25.5	225	16.1	14.9	0.13 (-0.06-0.31)

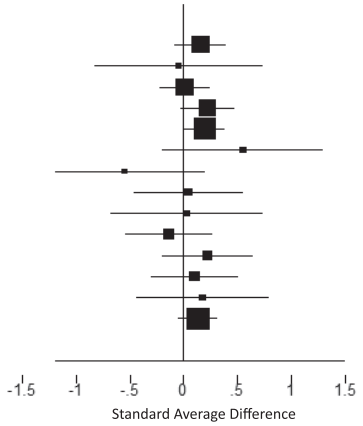

Figure 3. TGlobal survival time (months) according to the therapeutic regimens present in the studies included in the systematic review

Captions: Ref. – Number of the bibliographic reference; n – Quantity of participants per arm of the study; Med – Median of survival in months; SD – Standard Deviation; CI 95% – Confidence Interval of 95%; C – Cisplatin; P – Pemetrexed.
Nota: * —Valor imputado com a média dos desvios padrões dos outros estudos.

with the association cisplatin and pemetrexed (1.8%); Muers et al.[11], in the group that utilized specifically vinorelbine and supportive care (0.9%); and Zalcman et al.[16], with the association cisplatin, pemetrexed and bevacizumab. The regimens with higher toxicity scores 3 and 4 were gemcitabine associated to cisplatin (leukopenia – 38.1%; thrombocytopenia – 23.8%; nausea/vomit – 33%)[9]; cisplatin combined to pemetrexed (neutropenia – 23.2%[13] and 44.6%[16]); cisplatin in combination with pemetrexed and axitinib (neutropenia – 45%)[15] further to cisplatin in combination with pemetrexed and bevacizumab (neutropenia – 44.1% and hypertension – 23%)[16]; and cisplatin in combination with pemetrexed and nintedanib (neutropenia – 43.2%)[19].

DISCUSSION

It is still controversial what the best treatment for pleural mesothelioma is. A small proportion of patients is eligible for surgical management and, for most of them, the available include chemotherapy, radiotherapy or supportive treatment. However, debates are still held about the ideal chemotherapy regimen with an array of isolated agents and, more recently, immunotherapy-based strategies are being explored [22].

Chemotherapies regimens addressed in this revision were tested in participants without possibility of surgical treatment in nearly 90% of the randomized trials. Two clinical trials included patients who could be submitted to surgical intervention. In Buikhuisen et al.[15], the participants were randomized for two chemotherapy regimens: cisplatin + pemetrexed and cisplatin + pemetrexed + axitinib. The global survival time did not differ statistically and significantly in the groups (18.5 and 18.9 months, respectively)[15]. In Zauderer et al.[21], the participants were also randomized to two chemotherapy regimens: cisplatin + pemetrexed and cisplatin + pemetrexed + galinpepimut-S. The global survival time did not statistically and significantly differ among the groups on account of the number of participants of the Phase II study (18.3 and 22.8 months, respectively)[21]. Galinpepimut-S may become an option for the treatment of malignant pleural mesothelioma, in case a Phase III study is conducted with an extended number of participants.

Except for the study of E Habib et al.[9], all the others analyzed the global survival time. This work compare two regimens – cisplatin + gemcitabine (n=21) and carboplatine + pemetrexed (n=19) – and measured only the cumulative survival in one year and a half of follow up, corresponding to 41% and 57%, respectively[9]. For quality sake, this study was one that presented a very negative result.

The study of Kovac et al.[18] has also tested the combination cisplatin and gemcitabine. This combination was compared with cisplatin and pemetrexed. The participants where neoplasm progressed after chemotherapy could utilize the other treatment. The combination cisplatin and gemcitabine had a global survival mean lower than 18.6 months against 20.6 of the combination cisplatin and pemetrexed. The authors suggested that cisplatin and gemcitabine could be an option of second line treatment of the malignant pleural mesothelioma or, yet, first line treatment in the countries where pemetrexed is unavailable for the general population[18].

In the other studies, cisplatin and pemetrexed-based regimens associated to a third antineoplastic presented

the higher global survival times. The association of bevacizumab, cisplatin e pemetrexed (18.8 months, CI 95% (15.9-22.6), in the study of Zalcman et al.[16] , showed that the participants had better clinical condition and could utilize pemetrexed as a maintenance therapy[16]. This study had 448 patients, with less than 76 years and less than 10% presenting *performance status* 2. After a median follow up time of 39.4 months, patients who received bevacizumab associated to the combination pemetrexed + cisplatin had a median global survival time better than those who received only pemetrexed + cisplatin (18.8 *vs* 16.1 months, OR adjusted of 0.75 and p=0.0167). For quality wise, this study was one with the best result.

The study of Tsao et al.[20] utilized the combination cisplatin, pemetrexed and cediranib. This last, an inhibitor of the receptors of the vascular endothelial growth. After the use of the combination, the participants utilized cediranib as maintenance treatment. There were 92 participants with mean age of 72 years old. The global survival was 10 months against 8.5 months of combination cisplatin, pemetrexed and placebo. The numeric superiority did not reach, however, statistical significance (HR=0.84 and p=0.44). The global survival time lower than the other studies perhaps can be explained by the higher mean age of the participants[20].

Another inhibitor of the factor of vascular endothelial growth, nintedanib, was utilized in combination with cisplatin and pemetrexed in the study of Grosso et al. [19]. The Phase II clinical trial, randomized, double-blind counted with the participation of 87 patients. Only those with *performance status* 0 or 1 and epithelioid and biphasic tumors in the sample explain the high mean global survival times achieved. The participants who utilized the treatment with nintedanib had global survival time of 18.3 months against 14.2 months of the treatment cisplatin, pemetrexed and placebo. This result did not have statistical significance (HR=0.77 and p=0.319)[19].

The only therapeutic regimen that presented a significant positive standard mean difference in this systematic review, in terms of global survival, was that involving cisplatin associated to pemetrexed. The study of Volgezang et al.[13] randomized 448 patients to receive cisplatin alone *versus* its association to pemetrexed, showing better survival (12.1 *vs* 9.3 months, HR 0.77, p=0.02), but also bigger toxicity (neutropenia, thrombocytopenia, vomits and febrile neutropenia) of the combined regimen[13].

The systematic review of Ellis et al.[23] had already identified the regimen pemetrexed + cisplatin as the option with the best evidence of efficacy and safety with cisplatin + raltitrexed, being an alternative in cases where this option is not possible[23]. The Cochrane review evaluated specifically the efficacy of the combination pemetrexed + cisplatin, with complementation of folic acid and vitamin B12, in naive-treatment patients with pleural mesothelioma compared to other cytotoxic agents used isolated or combined and to the supportive care and also indicated improvement of the survival in patients with good *performance status*[24]. It is worth mentioning that both revisions identified only the study of Volgezang et al.[13] already mentioned to support these findings [13].

The combination carboplatine + pemetrexed showed mean global survival time of 13 months (CI 95% 5.6-21.9) when compared to the regimen gemcitabine + pemetrexed (6 months, CI 95% 3.9-14.0), but in a small Phase II study with only 29 participants[17]. The quality of this study could not be evaluated because it was an abstract for a congress. The study had patients in less severe conditions and was interrupted before the planned schedule. In a non-randomized study of an international expanded access program with 1,704 patients, carboplatine + pemetrexed and cisplatin + pemetrexed presented comparable efficacy and safety [25]. Carboplatine appears to be an option for patients who could not use cisplatin and vice-versa.

In relation to the safety of the therapeutic regimens, the use of antifolates increased the toxicity of the chemotherapy in comparison with the isolated use of cisplatin. The study of Arnold et al.[26], with 73 participants showed that pemetrexed + cisplatin and pemetrexed + carboplatine resulted in the worsening of the global health status compared to the active control of symptoms after 16 weeks[26]. Cisplatin + pemetrexed were associated to three deaths because of toxicity; in Vogelzang et al. [13], all the cases occurred before the supplementation with folic acid and vitamin B12. Ever since, this use became common in clinical practice whenever the regimen includes pemetrexed, with studies indicating that the addition improves the efficacy of the treatment, since the reduction of the adverse effects grants major number of cycles of chemotherapy and bigger global survival compared to those who did not receive the supplementation[27].

In Brazil, there is still no clinical trials or therapeutic guideline about the treatment of malignant pleural mesothelioma. A series of international clinical guidelines recommends the platin + antifolate derivative combination of as first choice option for the treatment of malignant pleural mesothelioma in cases where chemotherapy alone is possible and, also, in multimodal treatment. Cisplatin and pemetrexed are preferable over carboplatine and raltitrexede[2,23,24,28-30]. The last guidelines of the *American Society of Clinical Oncology,* of 2018, recommends the association premetrexede + platin (high quality of the evidence, with strong recommendation strength) as first line chemotherapy with the addition of bevacizumab and

can be considered in selected patients without counter-indication to the monoclonal antibody (high quality of evidence with moderate recommendation strength)[31]. These patients would be those with the type of epithelial mesothelioma with *performance status* 0-1, without significant cardiovascular disease without uncontrolled hypertension, less than 75 years old, no risk of bleeding or thrombus and with serum values of the factor of endothelial vascular growth below averages[31,32].

It draws the attention the reduced number of chemotherapy treatment-related of pleural mesothelioma identified in this review. The rarity of the condition and the inclusion criteria applied in the eligibility of the studies as the demand of having a control group, have possibly contributed for this situation. This finding strengthens the importance of conducting more clinical trials, most of all if considered the diagnosis in advanced staging, which limits the possibility of surgical treatment, and the expectation that the number of cases keeps at a significant level still for many years in the country, since not until November 2017, the Brazilian Supreme Court (STF) has prohibited the extraction, industrialization, commercialization and distribution of asbestos domestically[33].

Only in ten studies it was possible to evaluate the quality[9-16,19,21]. The others consisted of three abstracts presented in congresses[17,18,20]. The lack of proper blinding and the absence of a report about how the randomization process was done suggest the possibility of biases in the studies. Though it is recommended the inclusion of abstracts of congresses to avoid bias of publication, caution should be considered in using these references[34].

The present study has a few limitations. It is difficult to compare the results of the outcomes among studies that present differences in the average time of follow up, age, histology, *performance status*, among other factors. Because of being distinct therapeutic regimens, it was not possible to verify whether these factors objectively affect the prognosis of the disease. As such, there are risks of biases if comparisons of outcomes are attempted among the studies.

CONCLUSION

Future clinical trials about malignant pleural mesothelioma should utilize the double derivative of platin + antifolate as control group. The combination of cisplatine and pemetrexed is preferable over carboplatine and raltitrexed because it was more tested. The addition of bevacizumab to the derivative therapy of platin + antifolate, although it becomes to be the therapeutic options for less severe cases in the guideline of *American Society of Clinical Oncology,* still needs more studies.

In a disease with as poor a prognosis as might be possible as mesothelioma, any new treatment that promises palliation of the symptoms or increase of the survival may appear very appealing. However, to evaluate new therapies, it is important to consider what is the best option for these patients, taking into account the efficacy of the safety profile. Patients and healthcare providers should weigh the best efficacy of the use of platin derivatives combined with antifolates against the toxicity associated to these regimens. Clinical trials with proper methodology designs are important to be conducted. At last, in relation to the potential incorporation of technologies, economic assessments need to be made that may serve as bases for a better decision on the options for the chemotherapy treatment of the malignant pleural mesothelioma in each country.

CONTRIBUTIONS

André de Oliveira Souza participated of the conception, search in the databases, selection of articles, extraction of data, evaluation of the quality of the articles and final wording. Vera Lúcia Edais Pepe participated of the conception, search of the databases, evaluation of the quality of the articles and final wording. Lenice Gnocchi da Costa Reis participated of the conception, evaluation of the quality of the articles and final wording. Rosângela Caetano participated of the conception and final wording. Luiz Gustavo André Oliveira participated of the selection and extraction of data. All the authors approved the final version of the article.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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REFERENCES

1. Terra Filho M, Freitas JBP, Nery LE. Doenças asbesto-relacionadas. J Bras Pneumol. 2006;32(2 Suppl):S48-53. doi: http://dx.doi.org/10.1590/S1806-37132006000800009.
2. Pinto C, Novello S, Torri V, et al. Second Italian consensus conference on malignant pleural mesothelioma: state of the art and recommendations. Cancer Treat Rev. 2013;39(4):328-339. doi: https://doi.org/10.1016/j.ctrv.2012.11.004.
3. Bianchi C, Bianchi T. Malignant Mesothelioma: Global incidence and relationship with asbestos. Ind Health. 2007;45(3):379-387. doi: https://doi.org/10.2486/indhealth.45.379.

4. Iwatsubo Y, Pairon JC, Boutin C, et al. Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study. Am J Epidemiol. 1998;148(2):133-142. doi: https://doi.org/10.1093/oxfordjournals.aje.a009616.

5. Kazan-Allen L. Asbestos and mesothelioma: worldwide trends. Lung Cancer. 2005;49(1 Suppl):S3-8. doi: https://doi.org/10.1016/j.lungcan.2005.03.002.

6. Algranti E, Saito CA, Carneiro APS, et al. The next mesothelioma wave: mortality trends and forecast to 2030 in Brazil. Cancer Epidemiol. 2015;39(5):687-692. doi: https://doi.org/10.1016/j.canep.2015.08.007.

7. Zucali PA, De Vincenzo F, Simonelli M, et al. Future developments in the management of malignant pleural mesothelioma. Expert Rev Anticancer Ther. 2009;9(4):453-467. doi: https://doi.org/10.1586/era.09.2.

8. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions Version 5.1.0. London: Cochrane. [2006?]- [updated 2011Mar 20; cited 2018 Sept 13. Available from: https://training.cochrane.org/handbook.

9. Habib EE, Fahmy ES. Chemotherapy management of malignant pleural mesothelioma: a phase II study comparing two popular chemotherapy regimens. Clin Transl Oncol. 2013;15(11):965-968. doi: https://doi.org/10.1007/s12094-013-1015-3

10. Krug LM, Wozniak AJ, Kindler HL, et al. Randomized phase II trial of pemetrexed/cisplatin with or without CBP501 in patients with advanced malignant pleural mesothelioma. Lung Cancer. 2014;85(3):429-434. doi: https://doi.org/10.1016/j.lungcan.2014.06.008.

11. Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet. 2008 May17;371(9625):1685-1694. doi: https://doi.org/10.1016/S0140-6736(08)60727-8.

12. van Meerbeeck JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and The National Cancer Institute of Canada. J Clin Oncol. 2005;23(28):6881-6889. doi: https://doi.org/10.1200/JCO.20005.14.589.

13. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21(14): 2636-2644. doi: https://doi.org/10.1200/JCO.2003.11.136.

14. White SC, Anderson H, Jayson GC, et al. Randomised phase II study of cisplatin-etoposide versus infusional carboplatin in advanced non-small-cell lung cancer and mesothelioma. Ann Oncol. 2000;11(2):201-206. doi: https://doi.org/10.1023/A:1008328605413.

15. Buikhuisen WA, Scharpfenecker M, Griffioen AW, et al. A randomized phase II study adding axitinib to pemetrexed-cisplatin in patients with malignant pleural mesothelioma: a single-center trial combining clinical and translational outcomes. J Thorac Oncol. 2016;11(5):758-768. doi: https://doi.org/10.1016/j.jtho.2016.01.014.

16. Zaleman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2016;387(10026):1405-1414. doi: https://doi.org/10.1016/S0140-6736(15)01238-6.

17. Millenson MM, Lee J, Hanna NH, et al. Pemetrexed (Pem) plus gemcitabine (Gem) or carboplatin (Carbo) in patients (pts) with advanced malignant mesothelioma (MPM): A randomized phase II trial, E1B03. J Clinical Oncol. 2010;28(15 Suppl):e18053. doi: https://doi.org/10.1200/jco.2010.28.15_suppl.e18053.

18. Kovac V, Zwitter M, Strbac D, et al. Cisplatin with pemetrexed or gemcitabine in prolonged infusion for inoperable mesothelioma: a phase ii randomized trial. J Thorac Oncol. 2017;12(1 Suppl):S1362-S1363. doi: https://doi.org/10.1016/j.jtho.2016.11.1929.

19. Grosso F, Steele N, Novello S, et al. Nintedanib plus pemetrexed/cisplatin in patients with malignant pleural mesothelioma: phase II results from the randomized, placebo-controlled LUME-Meso Trial. J Clin Oncol. 2017;35(31):3591-3600. doi: https://doi.org/10.1200/JCO.2017.72.9012.

20. Tsao AS, Miao J, Wistuba II, et al. SWOG S0905: a randomized phase II study of cediranib versus placebo in combination with cisplatin and pemetrexed in chemonaive patients with malignant pleural mesothelioma. J Clin Oncol. 2018;36(15 Suppl):8514-8514. doi: https://doi.org/10.1200 / JCO.2018.36.15_suppl.8514.

21. Zauderer MG, Tsao AS, Dao T, et al. A randomized phase II trial of adjuvant galinpepimut-s, WT-1 analogue peptide vaccine, after multimodality therapy for patients with malignant pleural mesothelioma. Clin Cancer Res. 2017;23(24): 7483-7489. doi: https://doi.org/10.1158/1078-0432.CCR-17-2169.

22. Cinausero M, Rihawi K, Sperandi F, et al. Chemotherapy treatment in malignant pleural mesothelioma: a difficult history. J Thorac Dis. 2018 Jan;10(Suppl 2):S304-310. doi: https://doi.org/10.21037/jtd.2017.10.19.

23. Ellis P, Davies AM, Evans WK, et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. J Thorac Oncol. 2006;1(6):591-601. doi: https://doi.org/10.1016/S1556-0864(15)30366-X.

24. Green JA, Dundar Y, Dodd SR, et al. Pemetrexed disodium in combination with cisplatin versus other

cytotoxic agents or supportive care for the treatment of malignant pleural mesothelioma. *Cochrane Database Syst Rev*. 2007 Jan;(1): CD005574. doi: https://doi.org/10.1002/14651858.CD005574.pub2.

25. Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaïve patients with malignant pleural mesothelioma: results of the International Expanded Access Program. J Thorac Oncol. 2008;3(7):756-763. doi: https://doi.org/10.1097/JTO.0b013e31817c73d6.
26. Arnold DT, Hooper CE, Morley A, et al. The effect of chemotherapy on health-related quality of life in mesothelioma: results from the SWAMP trial. Br J Cancer. 2015;112(7):1183-1189. doi: https://doi.org/10.1038/bjc.2015.77.
27. Scagliotti GV, Shin DM, Kindler HL, et al. Phase II study of pemetrexed with and without folic acid and vitamin B12 as front-line therapy in malignant pleural mesothelioma. J Clin Oncol. 2003;21(8):1556-1561. doi: https://doi.org/10.1200/JCO.2003.06.122.
28. van Zandwijk N, Clarke C, Henderson D, et al. Guidelines for the diagnosis and treatment of malignant pleural mesothelioma. J Thorac Dis. 2013;5(6):E254-E307. doi: https://doi.org/10.3978/j.issn.2072-1439.2013.11.28.
29. Scherpereel A, Astoul P, Baas P, et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J. 2010;35(3):479-495. doi: https://doi.org/10.1183/09031936.00063109.
30. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26(5 Suppl):v31-v39. doi: https://doi.org/10.1093/annonc/mdv199.
31. Kindler HL, Ismaila N, Armato SG, et al. Treatment of malignant pleural mesothelioma: american society of clinical oncology clinical practice guideline. J Clin Oncol. 2018 May;36(13):1343-1373. doi: https://doi.org/10.1200/JCO.2017.76.6394.
32. Kondola S, Manners D, Nowak AK. Malignant pleural mesothelioma: an update on diagnosis and treatment options. Ther Adv Respir Dis. 2016;10(3) 275-88. doi: https://doi.org/10.1177/1753465816628800.
33. Dundar Y, Dodd S, Williamson P, et al. Case study of the comparison of data from conference abstracts and full-text articles in health technology assessment of rapidly evolving technologies: does it make a difference? Int J Technol Assess Health Care. 2006;22(3):288-294. doi: https://doi.org/10.1017/S0266462306051166.

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