Journal of Cancer Research and Clinical Oncology
https://doi.org/10.1007/s00432-022-04079-x

REVIEW – CLINICAL ONCOLOGY

Liposomal formulations for lung cancer treatment in the last two decades: a systematic review

Filipa Canão[1] · Helena Ferreira[2,3] · Nuno M. Neves[2,3]

Received: 2 November 2021 / Accepted: 19 May 2022
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Abstract

Purpose Lung cancer is the leading cause of cancer mortality worldwide. To improve the therapeutic outcomes, drug delivery systems, and particularly liposomes, have been widely investigated. Therefore, this review analyzed systematically the literature to inquire about the safety and efficacy of liposomal formulations in lung cancer treatment.

Methods Three electronic databases (PubMed, Web of Science and Cochrane CENTRAL) were systematically searched until May 2020. Clinical trials containing information about the effects of liposomal formulations in lung cancer patients were considered eligible.

Results Twenty two selected studies present different treatment options for both small and non-small-cell lung cancers. After compiling and analyzing all the published information, we verified that combination of liposomal cisplatin and paclitaxel led to a statistically significant improvement of the evaluated outcomes. Moreover, tecemotide, a liposome-based immunotherapy, demonstrated lower toxicity compared to control groups. Evidences that other subgroups could benefit from this formulation were also provided.

Conclusion This systematic review (registration number CRD42021246587) demonstrates that liposomal formulations are promising alternatives to overcome limitations of traditional cancer therapy. However, larger, longer, randomized and double-blinded clinical trials, selecting their patients' cohort considering more responsive subgroups would be beneficial to strengthen the scientific and clinical evidence of the results herein reported.

Keywords Lung cancer · Liposomal formulations · Drug delivery · Clinical trials · Efficacy · Adverse events

Introduction

Cancer is rapidly becoming the most important obstacle to the increase of life expectancy worldwide. Particularly, lung cancer is the most diagnosed, in both sexes, being the leading cause of cancer death (Sung et al. 2021). Moreover, it is mostly diagnosed in patients aged 65 and over at an advanced stage, due to late manifestation of its symptoms (Novello et al. 2016). These facts combined with the systemic and serious side effects of the available therapeutic approaches lead to a very poor prognosis, especially in certain subtypes of lung cancer (Novello et al. 2016).

The concept of tailoring the drugs dose to a specific patient—personalized or precision therapy—and the use of targeted drug delivery devices could provide the necessary breakthrough to improve the efficacy and safety of the currently available treatments (Sharma et al. 2017). Several promising and novel targeted therapies (Woodman et al. 2021) have been disclosed, but in this systematic review, we

✉ Helena Ferreira
helenaferreira@i3bs.uminho.pt

✉ Nuno M. Neves
nuno@i3bs.uminho.pt

[1] School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal

[2] 3B's Research Group, I3Bs Research Institute on Biomaterials, Biodegradables and Biomimetics, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, Avepark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, University of Minho, 4805-017 Barco/Guimarães, Portugal

[3] ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal

Published online: 04 June 2022

focused our analysis on liposomal formulations. Liposomal formulations may be applied as alternatives or add-ons for the current therapies to provide better clinical outcomes and increase the survival and the quality of life of the patients. Current anticancer drugs have a narrow therapeutic window, are very susceptible to changes in their bioavailability and biodistribution, which translates in severe adverse events (AEs) and can present lower efficacy if the ideal conditions are not provided (Giodini et al. 2017). Therefore, the development of liposomal formulations allows to overcome problems associated with the poor solubility and undesirable AE profile of the drugs that negatively impact the clinical outcomes (Sharma et al. 2017). Indeed, the value of these delivery systems is demonstrated by their translation into the clinic as well as their use in several and large clinical trials. Hence, the main purpose of this systematic review is to evaluate the efficacy and safety of liposomal formulations in lung cancer patients' treatment and compare their clinical outcomes with the available treatments. For that, the primary outcomes considered in this analysis were overall survival (OS), progression-free survival (PFS) and response rate (RR) and the secondary outcome was the AEs.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009).

Search strategy

Three electronic databases (Web of Science, PubMed and Cochrane CENTRAL) were used systematically from February to May 2020. The following keywords, Boolean operators, and combinations were used: [("lung neoplasms") OR "lung cancer") AND liposom* AND patient AND clinical]. An additional filter was used to select only the articles published in the last 20 years, more precisely, from 2000/01/01 to 2020/05/05. The systematic review was registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO) with the registration number of CRD42021246587.

Eligibility criteria

Clinical trials that addressed the efficacy and safety of liposomal formulations for lung cancer treatment were considered eligible. The selection of the manuscripts was performed based on inclusion/exclusion criteria listed in Table 1.

Study selection and quality appraisal

The records were independently screened and analyzed according to the inclusion and exclusion criteria by two reviewers (FS and HF) and posteriorly confirmed by a third independent reviewer (NMN). After this selection, full-text copies of every potentially relevant study were obtained. The articles that fulfilled these criteria were selected for this systematic review and, then, the methodological quality assessment for the comparative studies was directly retrieved from the Critical Appraisal Skill Program (CASP) Randomized Controlled Trial Checklist (CASP 2018) classifying them as high-, moderate- or poor-quality trials. Furthermore, the quality of the non-comparative studies was evaluated using the Methodological Index for Non-Randomized Studies form (MINORS) (Slim et al. 2003).

Data extraction

The information about the first author, year of publication, country, study design, sample size, nature of the sample (including age, gender and previous or concomitant treatments), type and stage of lung cancer, treatment regimen and the relevant results on the efficacy of each pharmacological approach according to the aforementioned primary outcomes (OS, PFS, RR) was extracted and organized into tables. To measure safety, data of the AEs of each study were also retrieved.

Table 1 Studies eligibility criteria

Inclusion criteria	Exclusion criteria
Population: Humans with a diagnosis of LC (primary or metastatic) Intervention: Treatment with liposomal formulations (regardless of other therapeutic approaches) Study design: RCTs or non-comparative studies with ≥ 15 eligible patients Study variables: At least one of the primary outcomes (OS, PFS or RR) Languages: English or Portuguese	Records that are reviews, meta-analysis, qualitative studies, case reports, editorials, meeting abstracts, opinions/comments, letters to editor, protocols and book chapters Other topics (not focusing on or not reporting clinical data with liposomes) Pre-clinical studies Published before 1 January 2000

LC Lung cancer, *RCTs* Randomized controlled trials, *OS* Overall survival, *PFR* Progression-free survival, *RR* Response rate

Results

Identification and selection

As shown in Fig. 1, of the 347 articles extracted from the selected databases, we excluded the duplicated ones (55) and the ones that did not meet the inclusion criteria (257) by analysis of the title and abstract. After this first screening, 13 studies were removed, by reading the full text, due to incomplete data (still ongoing or discontinued trials without published results) or by absence of the required outcomes. Consequently, only 22 articles were considered eligible for this systematic review, namely 8 comparative and 14 non-comparative studies.

Comparative studies

Studies characteristics

The characteristics of each trial and the summary of the relevant data gathered from the comparative studies included

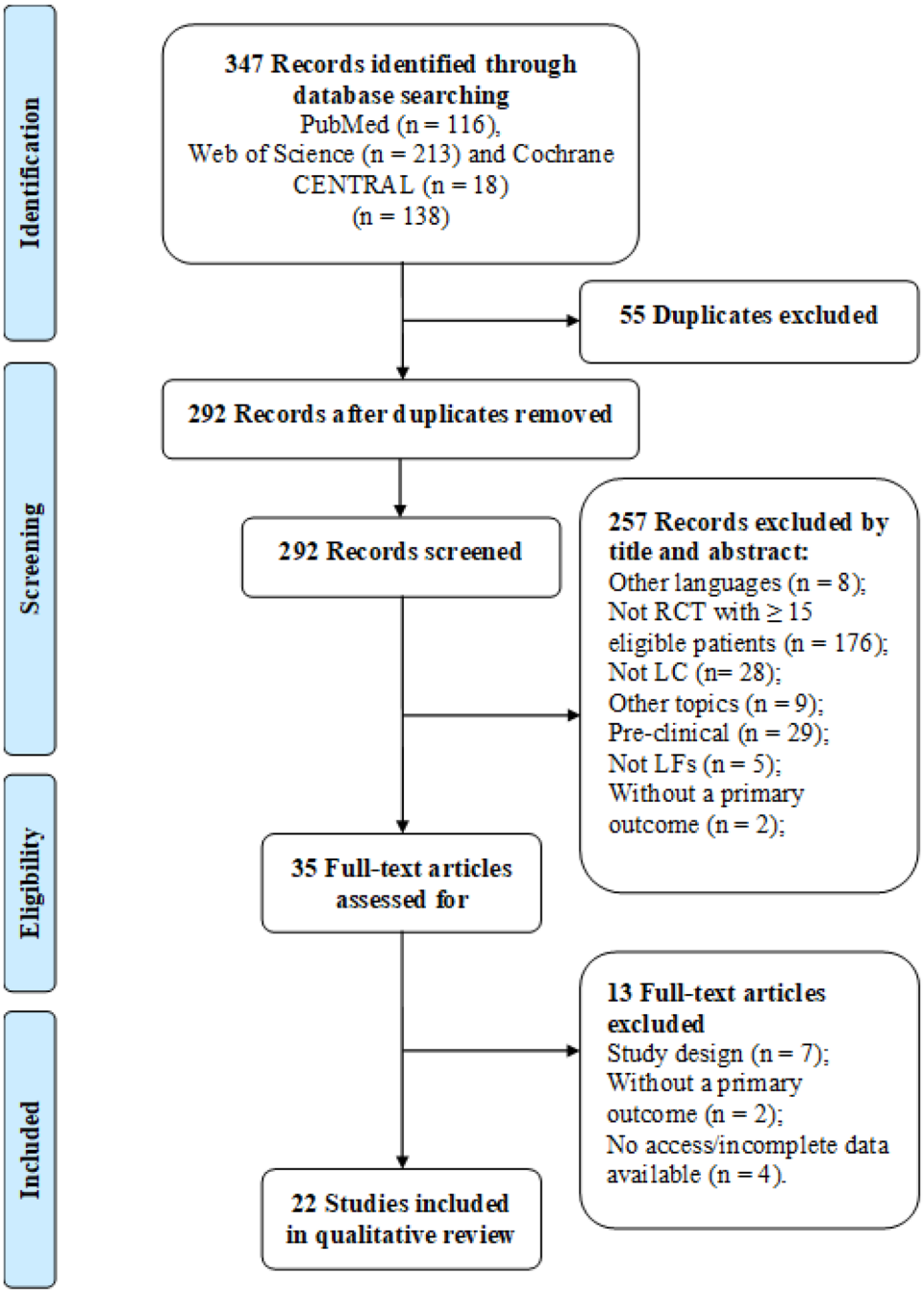


Fig. 1 PRISMA flow diagram of the literature search conducted in Pubmed, Web of Science and Cochrane CENTRAL

Table 2 Characteristics and outcomes of the included comparative studies

Study	Patients	Age	NSCLC	Treatment	Primary outcomes		
First author and year	Number	Median/range (years)	Stage		OS	PFS	RR
Katakami et al. (2017)	172	63.0/33–86	III	114 patients—single-dose of CPA (300 mg/m^2) + tecemotide (930 µg) vs 58 patients—saline + placebo; every week for 8 weeks, and, then, every 6 weeks[a]	No sig. improvement in the tecemotide group (32.4 vs. 32.2 months; $p = 0.83$)[b]	No difference between the treatment groups (p = NR)	NR
Mitchell et al. (2015) (update of previous trial) (Butts et al. 2014)	1239	61.0/19–89	III-IV	829 patients—tecemotide (806 µg) vs 410 patients—saline + placebo; every week for 8 weeks, and, then, every 6 weeks[a]	No sig. improvement in the tecemotide group (25.8 vs. 22.4 months; $p = 0.111$)[b]	NR	NR
Butts et al. (2014)	1239	61.0/19–89	III	829 patients—single-dose of CPA (300 mg/m^2) + tecemotide (806 µg) vs 410 patients—saline + placebo; every week for 8 weeks, and, then, every 6 weeks[a]	No sig. improvement in the tecemotide group (25.6 vs. 22.3 months; $p = 0.123$)[b]	NR	NR
Butts et al. (2011) (update of previous trial) (Butts et al. 2005)	171	59/(NR)	IIIB-IV	88 patients—single-dose of CPA (300 mg/m^2) + tecemotide (930 µg) + BSC vs 83 patients—BSC; every week for 8 weeks, and, then, every 6 weeks	There was an improvement in the tecemotide + BSC group (17.2 vs. 13.0 months; p = NR)	NR	NR
Stathopoulos et al. (2011) (update of previous trial) (Stathopoulos et al. 2010)	202	65/37–82	IIIB-IV	103 patients—L-cisplatin (200 mg/m^2) + paclitaxel (135 mg/m^2) vs 99 patients—cisplatin (75 mg/m^2) + paclitaxel (135 mg/m^2); every 2 weeks	No sig. improvement in the L-cisplatin + paclitaxel group (10 vs. 8 months; $p = 0.1551$)[b]	NR	PR was sig. improved in the L-cisplatin + paclitaxel group (59.22 vs. 42.42%; $p = 0.036$)[b] No patients achieved CR in either of the groups
Stathopoulos et al. (2010)	229	65.5/37–85	III-IV	114 patients—L-cisplatin (200 mg/m^2) + paclitaxel (135 mg/m^2) vs 115 patients—cisplatin (75–100 mg/m^2) + paclitaxel (135–175 mg/m^2); every 2 weeks (up to 9 cycles)	No sig. improvement in the L-cisplatin + paclitaxel group (9 vs. 10 months; $p = 0.577$)[b]	NR	No sig. difference between the treatment groups (58.8 vs. 47.0%; $p = 0.073$)

Table 2 (continued)

Study	Patients	Age	NSCLC	Treatment	Primary outcomes		
First author and year	Number	Median/range (years)	Stage		OS	PFS	RR
Mylonakis et al. (2010)	88	65/49–83	IIIB-IV	47 patients—lipogem group—L-cisplatin (120 mg/m^2) + gemcitabine (1000 mg/m^2) vs 41 patients—CisGem group—cisplatin (100 mg/m^2) + gemcitabine (1000 mg/m^2); every 21 days (up to 6 cycles)	There was an improvement in the LipoGem group (12.8 vs. 10.8 months; p = NR)[b]	There was an improvement in the LipoGem group (7.5 vs. 6.5 months; p = NR)[b]	No sig. difference between the treatment groups (31.7 vs. 25.6%; $p = 0.411$) No patients achieved CR in either of the groups
Butts et al. (2005)	171	59/(NR)	IIIB-IV	88 patients—single-dose of CPA (300 mg/m^2) + tecemotide (1000 µg) + BSC Vs 83 patients—BSC; every week for 8 weeks, and, then, every 6 weeks	No sig. improvement in the tecemotide + BSC group (17.4 vs. 13 months; $p = 0.066$)[b]	NR	There was an improvement in the tecemotide + BSC group, (55.7 vs. 54.2; p = NR)[b]

BSC Best supportive care, *CPA* Cyclophosphamide, *CR* Complete response, *LC* Lung cancer, *L* Liposomal, *NR* Not reported, *NSCLC* Non-small-cell lung cancer, *OS* Overall survival, *PR* Partial response, *p p* value, *PFS* Progression-free survival, *RR*

Response rate, *sig*. significant, *vs*. versus

[a]Until disease progression or treatment withdrawal

[b]Compared to the placebo/control group

in this systematic review are shown in Table 2 (Butts et al. 2005, 2011, 2014; Mylonakis et al. 2010; Stathopoulos et al. 2010, 2011; Mitchell et al. 2015; Katakami et al. 2017). As shown, the trials were published between 2000 and 2017. In these comparative studies, a total of 1899 patients were evaluated, 1192 in the experimental group and 707 in the control group.

Five studies of the selected randomized controlled trials (RCTs) evaluated the use of tecemotide (previously identified as L-BLP25 or Stimuvax®, for instance). This liposome-based, antigen-specific cancer immunotherapy was designed to elicit a cellular immune response against Mucin 1 (MUC1) (Wurz et al. 2014) as an add-on to the patients' previous regimens or as maintenance treatment for patients with advanced NSCLC (Butts et al. 2005, 2011, 2014; Mitchell et al. 2015; Katakami et al. 2017). The other three comparative trials assessed the combination of liposomal cisplatin (L-cisplatin, also known as lipoplatin) with either paclitaxel (Stathopoulos et al. 2010, 2011) or gemcitabine (Mylonakis et al. 2010) as a first-line treatment alternative to the highly toxic free cisplatin for patients with advanced NSCLC.

Quality assessment

All comparative studies (Butts et al. 2005, 2011, 2014; Mylonakis et al. 2010; Stathopoulos et al. 2010, 2011; Mitchell et al. 2015; Katakami et al. 2017) were screened for quality assessment using the appropriate CASP checklist (CASP 2018): 7 were classified as high quality (Butts et al. 2005, 2011, 2014; Stathopoulos et al. 2010, 2011; Mitchell et al. 2015; Katakami et al. 2017) and only 1 as moderate-quality trial (Mylonakis et al. 2010) (SI, Table S1). Despite 7 being considered high-quality trials, some aspects of the works could be improved by introducing a blind trial design or by providing more complete information (Butts et al. 2005, 2011, 2014; Mylonakis et al. 2010; Stathopoulos et al. 2010, 2011; Mitchell et al. 2015), which can lead to bias in our analysis of the outcomes reported. Additionally, all of them provide a summary of the baseline characteristics of the studied population, but they fail to provide a statistical analysis (e.g., p value) of the differences between these properties that could be translated into an unbalanced and unrepresentative sample.

Efficacy

Three (Butts et al. 2014; Mitchell et al. 2015; Katakami et al. 2017) of the five (Butts et al. 2005, 2011, 2014; Mitchell et al. 2015; Katakami et al. 2017) RCTs that evaluated the efficacy of liposome-encapsulated tecemotide are placebo-controlled. The best supportive care (BSC) available for the patients was the control for the other two trials (Butts et al. 2005, 2011). Two of them update the data and analysis (Butts et al. 2011; Mitchell et al. 2015) of previous trials (Butts et al. 2005, 2014). At the beginning of the trials, all the patients in the experimental treatment groups received an infusion of cyclophosphamide (CPA—to inhibit suppressor T cells and enhance the response to the experimental treatment) 3 days before the vaccine. In a direct comparison between tecemotide plus BSC to BSC alone, no significant improvement in OS was obtained (Butts et al. 2011). However, this work showed an improvement in RR in the tecemotide group, without statistical significance (p value < 0.05). This work updates the previous OS (Butts et al. 2005) and unfortunately confirmed the initial results. Nonetheless, it was shown a clear trend toward an improvement in OS in the tecemotide group when compared to the BSC group. The results also demonstrated that the survival rate of the subgroup of patients with stage IIIB loco-regional lung cancer was significantly improved with the tecemotide plus BSC regimen when compared to BSC alone. No significant differences were observed between the treatment groups in OS in (Butts et al. 2014). Even after 20 months of additional observation beyond the primary analysis, the same conclusion was obtained by (Mitchell et al. 2015). There was a tendency for OS increase, but without statistical significance. However, they also evaluated some interesting subgroups that proved to be significantly improved by tecemotide when compared to the placebo group, namely concurrent chemoradiotherapy (QRT; p value $= 0.0066$); high soluble MUC1 levels (sMUC1; p value $= 0.0013$) and in the high antinuclear antibodies subgroup (ANA; p value $= 0.0005$). Lastly, Katakami et al. (Katakami et al. 2017) did not meet its primary objective of showing an increasing trend of OS since there was no significant improvement in the tecemotide group compared to the placebo group. Likewise, there was no difference between the groups for the PFS.

The remaining RCTs assessed the efficacy of L-cisplatin administered together with either paclitaxel (Stathopoulos et al. 2010, 2011) or gemcitabine (Mylonakis et al. 2010). For the control group, the trials used the same combination, but with cisplatin. Again, one of the trials (Stathopoulos et al. 2011) was an update of a previous one (Stathopoulos et al. 2010).

An improvement in both OS and PFS was observed in the L-cisplatin plus gemcitabine group when compared with the cisplatin + gemcitabine group (Mylonakis et al. 2010). However, the information provided does not allow to determine if the differences are significant. Moreover, no statistically significant differences in RR were observed between the treatment groups.

Stathopoulos et al, 2010 (Stathopoulos et al. 2010) presented no significant differences between the studied groups either in OS and RR. The OS was even objectively smaller in the L-cisplatin plus paclitaxel than the control. The update

of this study provided by Stathopoulos et al. (2011) inverted this last observation in the OS. The update also showed statistically significant superiority of the experimental group over the control group regarding RR in less than a year. It is also important to notice that these two trials (Stathopoulos et al. 2010, 2011) only addressed non-squamous cell lung cancer.

Safety

The major treatment-related AEs (grade ≥ 3) (Institute 2020) for patients with advanced NSCLC were explored considering the information provided by the trials. The goal was to acquire enough information to compare the toxicity between the treatment groups and possible related deaths, as is shown in Tables 3 and S2 (SI).

Overall, the patients in the tecemotide-related trials (Butts et al. 2005, 2011, 2014; Mitchell et al. 2015; Katakami et al. 2017) exhibited similar adverse responses in both treatment groups. Regarding the percentage of AEs related to the studied drug (adjusted to the sample size of the different groups), a lower percentage of major AEs is observed in the tecemotide treatment group (Table 3). The cause of death of the patient in the control group of Butts et al. 2014 (Butts et al. 2014) was not determined in the study.

In the RCTs evaluating L-cisplatin and paclitaxel formulations (Stathopoulos et al. 2010, 2011), it is noticeable an increasing trend of the number of major AEs in the control group of cisplatin plus paclitaxel. Focusing on the percentage of AEs related to the studied drugs, we can clearly ascertain that the patients in the control groups of these two trials showed a higher number of major AEs than those in the L-cisplatin plus paclitaxel treatment groups. There was no information about the relation of the AEs and deaths that occurred.

For L-cisplatin and gemcitabine-related trials, the most frequent and major AEs as well as their incidence in the respective treatment groups were registered in the study of Mylonakis et al. 2010. As can be observed in Table S2 (SI), there is a higher incidence of the reported AEs in the control group of this trial than in the treatment group. Notwithstanding, no treatment-related deaths were reported.

Non-comparative studies

Studies characteristics

The summarized characteristics of the 14 included non-comparative studies are presented in Table 4 (Vokes et al. 2000; Palmer et al. 2001; Numico et al. 2002; Leighl et al. 2003, 2006; Patlakas et al. 2005; White et al. 2006; Ravaioli et al. 2009; Butts et al. 2010; Wang et al. 2010; Xenidis et al. 2011; Lu et al. 2015; Chen et al. 2018; Lv et al. 2019). The trials were published between 2000 and 2019 and the sample size ranged from 12 to 52 patients out of a total of 364 patients evaluated.

Of the selected non-comparative studies, 11 (Vokes et al. 2000; Numico et al. 2002; Patlakas et al. 2005; Leighl et al. 2006; White et al. 2006; Butts et al. 2010; Wang et al. 2010; Lu et al. 2015; Chen et al. 2018; Lv et al. 2019) focused on various treatments for NSCLC, most of them as first-line alternatives (Palmer et al. 2001; Numico et al. 2002; Patlakas et al. 2005; White et al. 2006; Ravaioli et al. 2009; Wang et al. 2010; Chen et al. 2018; Lv et al. 2019) alone (Numico

Table 3 Overview of the major AEs in seven of the comparative studies

AEs	Groups, *n*			
	Tecemotide (Butts et al. 2005, 2011, 2014; Mitchell et al. 2015; Katakami et al. 2017) (*n* = 1582)		L-cisplatin + paclitaxel (Stathopoulos et al. 2010, 2011) (*n* = 229)	
	T (*n* = 1031)	C (*n* = 551)	T (*n* = 114)	C (*n* = 115)
Any ≥ grade 3[a]	394	211	NR	NR
Any ≥ grade 3[a] related to study drug	48	38	57	90
Any deaths	46	35	63	65
Any deaths related to study drug	0	1[b]	NR	NR
Events (%)				
Any	38.22%	38.29%	NR	NR
Studied drug	4.66%	6.90%	50.00%	78.26%

AEs Adverse events, *C* Control, *L* Liposomal, *n* number (patients), *NR* Not reported, *T* Treatment

[a]According to the National Cancer Institute Common Terminology Criteria, version 6.0. (CTCAE) (Institute 2020)

[b]Unknown cause

Table 4 Characteristics and outcomes of the selected non-comparative studies

Study	Patients	Age	LC	Treatment	Primary outcomes		
Author and year	Number	Median/range (years)	Subtype/stage		OS	PFS	RR
Lv et al. (2019)	52	61.0/32–75	NSCLC/IIIB-IV	L-paclitaxel (100 mg/m^2), + nedaplatin (50 mg/m^2); every 4 weeks for 2–6 cycles	16 months (95% CI 14.1–17.9)	8.5 months (95% CI 7.8–9.2)	38.5% No patients achieved CR (95% CI NR)
Chen et al. (2018)	38	62.0/51–67	NSCLC/II-IV	L-paclitaxel (60 mg/m^2) + carboplatin (AUC2); every week, for 6 weeks at most	29 months (95% CI NR)	17 months (95% CI NR)	68% (95% CI NR)
Lu et al. (2015)	48	60.0/41–71	NSCLC/III	L-paclitaxel (intratumoral 1–3 mg/ml injection) + carboplatin (AUC5) + gemcitabine (1000 mg/m^2); every 3 weeks[a]	23.2 months (95% CI 20.0–26.3)	16.5 months (95% CI 13.7–19.2)	81% (95% CI NR)
Butts et al. (2010)	22	58.2/NR	NSCLC/III	Tecemotide (1000 µg) + BSC; every week for 8 weeks, and, then, every 6 weeks[a]	Could not be estimated (8 deaths);	NR	NR
Xenidis et al. (2011)	31	64.0/48–67	SCLC	PLD (15 mg/m^2) + irinotecan (125 mg/m^2); every 4 weeks	3.16 months (95% CI NR)	NR	12.9% (95% CI 1.1–24.7%); no patients achieved CR

BSC Best supportive care, *CI* Confidence interval, *CPA* cyclophosphamide, *CR* Complete response, *D* Day, *LC* Lung cancer, *L* Liposomal, *NR* Not reported, *NSCLC* Non-small-cell lung cancer, *OS* Overall survival, *PR* Partial response, *PLD* pegylated L-doxorubicin, *PFS* Progression-free survival, *RR* Response rate, *SCLC* Small-cell lung cancer, *sig*. significant, *vs*. versus, *SPI-77* Sterically stabilized L-cisplatin

[a]Until disease progression or treatment withdrawal

et al. 2002; White et al. 2006; Wang et al. 2010; Xenidis et al. 2011) or combined with other available chemotherapeutic drugs (Numico et al. 2002; Patlakas et al. 2005; Lu et al. 2015; Chen et al. 2018; Lv et al. 2019), and others as add-on to the patients BSC (Butts et al. 2010) or as maintenance treatment (Palmer et al. 2001).

They also studied different routes of administration of liposomal formulations, namely subcutaneous (Palmer et al. 2001; Butts et al. 2010), intravenous (Chen et al. 2018; Lv et al. 2019), intratumoral (Lu et al. 2015) and a single infusion in the pleural cavity (Wang et al. 2010). The remaining 3 (Leighl et al. 2003, 2006; Xenidis et al. 2011) were based on the treatment of SCLC.

The studies that addressed the treatment of NSCLC tested different combinations of L-paclitaxel (liposomal paclitaxel) with other current available treatments, such as nedapine (Lv et al. 2019), carboplatin (Chen et al. 2018), and a combination with carboplatin and gemcitabine (Lu et al. 2015). Tecemotide was also investigated in two trials (Palmer et al. 2001; Butts et al. 2010) but only one also provided BSC (Butts et al. 2010). Other studies tested pegylated liposomal doxorubicin (PLD; also known as Caelyx®) alone (Numico et al. 2002), or in a combined triple therapy (Palmer et al. 2001) with docetaxel and gemcitabine. Three trials evaluated two different types of liposomal formulations, L-cisplatin (Ravaioli et al. 2009) and its sterically stabilized form—SPI-77 (Vokes et al. 2000; White et al. 2006), alone or in combination with vinorelbine.

Concerning the trials that focused on the treatment of SCLC, two of them evaluated the efficacy of the triple combination of PDL with CPA and vincristine (Leighl et al. 2003, 2006), but the most recent (Leighl et al. 2006) adjusted the dosages to decrease the drugs toxicity. The other trial also investigated PDL, but in combination with irinotecan (Xenidis et al. 2011).

Quality assessment

Regarding the quality of the 14 non-comparative studies (Vokes et al. 2000; Palmer et al. 2001; Numico et al. 2002; Leighl et al. 2003, 2006; Patlakas et al. 2005; White et al. 2006; Ravaioli et al. 2009; Butts et al. 2010; Wang et al. 2010; Xenidis et al. 2011; Lu et al. 2015; Chen et al. 2018; Lv et al. 2019), using the MINORS form (Slim et al. 2003): 5 were classified as high-quality (Numico et al. 2002; Leighl et al. 2006; Xenidis et al. 2011; Lu et al. 2015; Lv et al. 2019) and 9 as moderate-quality trials (Vokes et al. 2000; Palmer et al. 2001; Leighl et al. 2003; Patlakas et al. 2005; White et al. 2006; Ravaioli et al. 2009; Butts et al. 2010; Wang et al. 2010; Chen et al. 2018) (SI, Table S4). The main weakness observed is the lack of blinding in the clinical trials. Moreover, none of them provided explanations about the reasons of the selection of the studies management, exposing the trials to a possible risk of bias. Another item to take into consideration is the absence of confidence intervals (CI = 95%), and without it, we are not provided with range of values that are likely to be included the studied outcomes, nor the amount of random error in each sample.

Efficacy

NSCLC The trials that focused on L-paclitaxel showed promising results with noticeable improvements in the treatment groups for all the outcomes considered (Tables 4). OS ranged from 16 to 29 months, PFS from 8.5 to 17 months and RR from 38.5 to 90.9%. In the study of Chen et al. 2018 (Chen et al. 2018), a combination of L-paclitaxel with carboplatin was administered, being the trial with the overall best results. Although Lu et al. 2015 achieved the highest RR with the triple combination of L-paclitaxel, carboplatin, and gemcitabine, administered directly into the tumor.

For Tecemotide, only one of the trials, Palmer et al. 2001 (Palmer et al. 2001), determined RR successfully (15.8%). Indeed, Butts et al. 2010 (Butts et al. 2010) were not able to estimate the outcomes due to the high number of deaths in a small sample of patients. Palmer et al. 2001 (Palmer et al. 2001) also showed an improvement in the OS, mainly in the group receiving the highest vaccine dose.

The triple combination of PDL, docetaxel and gemcitabine used in Patlakas et al. 2005 (Patlakas et al. 2005), provided better results than PDL alone, as seen in Numico et al. 2002 (Numico et al. 2002), either in OS (11 months vs. 4.65 months), as well as in RR (10 vs 5.8%).

The two different formulations of L-cisplatin presented improvements in the treatment groups either in OS, which ranged from 5.75 to 7.2 months, as well as in RR, ranging from 4.5 to 15.8%. However, the highest RR was achivied by Vokes et al. 2000 (Vokes et al. 2000), using the combination of SPI-77 with vinorelbine, but information about OS was not assessed. Conversely, the highest OS was achieved in the study of Ravaioli et al. 2009 (Ravaioli et al. 2009) that investigated the efficacy of the non-sterically stabilized L-cisplatin.

SCLC The trials regarding SCLC treatment with PDL presented OS in the range between 3.16 and 7 months. Xenidis et al. 2011 investigated the efficacy of PDL formulation combined with irinotecan and presented the lowest OS of the three studies. The highest RR, which ranged from 10 to 24% was provided by the combination of PLD, CPA and vincristine in the study of Leighl et al, 2003 (Leighl et al. 2003). Nevertheless, only Leighl et al. 2006 (Leighl et al. 2006) provided the adequate 95% CI with the same combination, but at lower dosages. This last trial also presented the highest OS.

Safety

The major treatment-related AEs observed in the non-comparative trials are listed in Table 5. The most frequently observed AE was asthenia (9.38%), but neutropenia (8.49%), gastrointestinal tract toxicity (6.98%; e.g., nausea, diarrhea, constipation and esophagitis), leukopenia (5.5%), hepatotoxicity (4.95%), and anemia (2.95%) were also reported. The only trial that attributed causality of a reported death to the toxicity of the treatment administered was Numico et al 2002 (Numico et al. 2002). The patient died from an uncommon AE related to PLD. The remaining trials stated that the reported deaths were not related to the experimental treatments, but to the disease progression.

Discussion

Due to the prevalence and high mortality of lung cancer (Sung et al. 2021), as well as of the serious adverse effects of the current available treatments (Weiss et al. 1990), there is an urgent need for effective and safer alternative approaches.

Liposomes are being widely and successful used to overcome the main limitations of the current treatments. Indeed, these sphere-shaped phospholipid bilayers are non-toxic, biocompatible, biodegradable, and non-immunogenic carriers that can be used for systemic and local administration of chemotherapeutical drugs, reducing their toxicity and elimination rate, prolonging, consequently, their efficacy (Bulbake et al. 2017).

In this systematic review, the literature related to liposomal formulations was reviewed and although there are reviews that address the use of liposomal formulations in other types of cancer (Lawrie et al. 2013), to our knowledge,

Table 5 Overview of the major treatment-related AEs (≥ grade 3)[a] in the non-comparative studies

Study	Leukopenia	Neutropenia	Anemia	Hepato-toxicity	GI toxicity	Asthenia
Lv et al. (2019)	NR	7	4	NR	0	NR
Chen et al. (2018)	3	2	0	NR	3	NR
Lu et al. (2015)	NR	7	2	3	4	NR
Butts et al. (2010)	NR	NR	NR	NR	0	1
Xenidis et al. (2011)	NR	2	1	NR	1	7
Wang et al. (2010)	NR	0	0	1	0	NR
Ravaioli et al. (2009)	NR	NR	0	NR	0	0
White et al. (2006)	0	0	0	NR	4	NR
Leighl et al. (2006)	NR	2	NR	NR	5	5
Patlakas et al. (2005)	NR	0	NR	NR	NR	0
Leighl et al. (2003)	NR	NR	NR	1	4	2
Numico et al. (2002)	0	NR	0	NR	3	3
Palmer et al. (2001)	2	NR	0	NR	0	0
Vokes et al. (2000)	1	3	1	0	0	0
Events, *n* %	6, 5.50%	23, 8.49%	8, 2.95%	5, 4.95%	24, 6.98%	18, 9.38%
Total, *n*	109	273	271	101	344	192

AEs Adverse events, *n* number, *NR* Not reported, *TCP* Thrombocytopenia, *GI* Gastrointestinal

[a]According to the National Cancer Institute Common Terminology Criteria, version 6.0. (CTCAE) (Institute 2020)

this is the first systematic review focused on investigating the efficacy and safety of liposomal formulations in lung cancer treatment in the last 20 years.

After selecting 22 studies and extracting the relevant information, we assessed the efficacy of the evaluated formulations to treat either NSCLC or SCLC by analyzing the OS, PFS and RR. To assess their safety, we collected all the data relative to the treatment-related AEs, such as reported deaths. As described in the comparative trials results, from the tested drugs, the only trial that presented significant improvement, regarding the primary outcomes, was Stathopoulos et al. 2011 (Stathopoulos et al. 2011). Indeed, the combination of L-cisplatin with paclitaxel improved the treatment of patients with stage IIIB-IV NSCLC. This study demonstrated that the administered combination significantly improved the RR in the experimental group when compared to the control group. The trials that assessed the safety of this combination (Stathopoulos et al. 2010, 2011), presented a higher percentage of major AEs in their control groups than in their experimental groups. Consequently, we can ascertain that the combination of L-cisplatin with paclitaxel presents a lower toxicity than the regular combination of cisplatin with paclitaxel.

It was previously stated (Boulikas 2009) that L-cisplatin is "anticipated to become an important addition to the arsenal of anticancer drugs". Additionally, a study investigating the viability of new liposomal formulations (Menon et al. 2017) demonstrated that this combination of L-cisplatin with paclitaxel could be provided simultaneously in dual-drug containing nanoparticles for lung cancer treatment. Nevertheless, even if the evaluated treatments did not show superiority in terms of efficacy compared with the free drug group, not only do they provide the same results as current therapies, they also decrease toxicity, improving the patients' quality of life. Mitchell et al 2015 (Mitchell et al. 2015), Butts et al 2014 (Butts et al. 2014) and Butts et al 2005 (Butts et al. 2005) did not show a significant improvement in the OS and RR for NSCLC patients treated with tecemotide when compared to their respective control groups. A similar result was obtained by Stathopoulos et al 2010 (Stathopoulos et al. 2010) in the comparison of the OS provided by the combination of L-cisplatin and paclitaxel with the OS of the group treated with cisplatin. Despite they did not improve drug efficacy, the percentage of major AEs in the tecemotide treatment group was lesser than in its control groups. The same behavior was obtained for the L-cisplatin and paclitaxel combination that showed a steep decline in toxicity when compared to the AEs of the cisplatin group. Consequently, these two treatments seem to be viable options for the treatment of NSCLC.

Although the other comparative trials did not achieve statistical significance in their overall results, some of them brought to light some interesting conclusions in their analyzed subgroups, providing important insights for future study designs. Mitchell et al. (2015) showed a significant improvement with tecemotide in certain subgroups, such as patients that received concurrent QRT and presented high sMUC1 or ANA levels, when compared to the control groups. This evidence helps to define the patient populations

that can have the greatest benefit possible of the treatment with liposomal formulations and determining the best combination of drugs in future trials.

In the non-comparative studies, we concluded that there are many promising liposomal formulations that led to the improvement of therapy efficacy and to the decrease of toxicity both in NSCLC and SCLC. Unfortunately, their small samples, unblinded nature and missing CIs, require better designed trials to test these liposomal formulations.

The high quality of non-comparative studies, as evaluated by the MINORS form (Slim et al. 2003), were the ones that assessed the considered outcomes and provided the respective CIs, namely Lv et al. (2019) with the combination of L-paclitaxel and nedaplatin (OS, PFS and RR); Lu et al. 2015 with the intratumoral administration of L-paclitaxel combined with carboplatin and gemcitabine (OS and PFS); Xenidis et al. 2011 with the combination of PLD and irinotecan (RR); (Leighl et al. 2006) with the triple combination of PLD, CPA and vincristine (OS and RR); and Numico et al. (2002) with the sterically stabilized version of L-cisplatin (RR). Regarding safety, the most frequent major treatment-related AEs reported with these treatments, proved to be less severe than those commonly observed with the free drug.

Another limitation is the lack of assessment of PFS in the majority of the analyzed trials. Even though it is a rather new outcome variable, PFS provides information not only related to responsive disease, but also to stable disease. This is particularly important considering the need to evaluate if these liposomal formulations confer a survival advantage in lung cancer patients, even if the therapies provide minimal to null response (Villaruz et al. 2013). Additionally, larger, longer, and double-blinded clinical trials, would be beneficial to strengthen the previous results and overcome the limitations of the reviewed studies.

Conclusion

The highest-quality trials selected demonstrated that only the combination of L-cisplatin and paclitaxel led to a significant improvement of the evaluated outcomes, with the lowest toxicity in patients with NSCLC. Therefore, this formulation is safer and more effective than traditional chemotherapy. Moreover, tecemotide should be seriously considered in the NSCLC treatment as it decreases toxicity, while providing a similar efficacy when compared to the control group. Further clinical trials should also be conducted to investigate the efficacy of liposome formulations in certain subgroups (concurrent QRT and high sMUC1 and ANA levels).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-022-04079-x.

Funding Not applicable.

Declarations

Conflict of interest Authors have no conflicts of interest.

Availability of data and material Not applicable.

Code availability Not applicable.

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