Lung Cancer 126 (2018) 25–31

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Systemic treatments for thymoma and thymic carcinoma: A systematic review☆

Thierry Berghmans[a,j,*], Valérie Durieux[b], Stéphane Holbrechts[c], Christiane Jungels[d], Jean-Jacques Lafitte[e], Anne-Pascale Meert[a], Luigi Moretti[f], Sebahat Ocak[g,h], Martine Roelandts[f], Nicolas Girard[i]

[a] Department of Intensive Care and Oncological Emergencies & Thoracic oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[b] Bibliothèque des Sciences de la Santé, Université libre de Bruxelles, Belgium
[c] Department of Oncology, CHU Ambroise Paré Mons, Belgium
[d] Department of Oncological Medicine and Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[e] Université de Lille, Lille, France
[f] Department of Radiotherapy, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[g] Division of Pneumology, CHU UCL Namur (Godinne Site), Université catholique de Louvain (UCL), Yvoir, Belgium
[h] Institut de Recherche Expérimentale et Clinique (IREC), Pôle de Pneumologie, ORL et Dermatologie (PNEU), UCL, Brussels, Belgium
[i] Institut du Thorax Curie Montsouris, Institut Curie, Paris, France
[j] Laboratoire Facultaire de Médecine Factuelle de l'Université Libre de Bruxelles, Belgium

ARTICLE INFO

Keywords:
Thymoma
Thymic carcinoma
Chemotherapy
Systematic review

ABSTRACT

Thymic tumours are rare diseases that for most of the cases are cured with surgery and eventually adjuvant radiotherapy. However, about 30% of patients present with advanced stage or relapsing tumours, which require administration of chemotherapy. While cisplatin-adriamycin-cyclophosphamide combination is regularly prescribed, other drugs have been assessed in the literature. Our aim is to evaluate the effectiveness (response rate) of systemic treatments, whatever the therapeutic line, including chemotherapy, targeted therapies and immunotherapies, in thymoma and thymic carcinoma, using the principles of evidence-based medicine. A systematic review was designed using the PICO system, by an experienced librarian and clinicians' experts in thoracic oncology, through the Ovid Medline system. Only phase II-IV trials and retrospective studies including at least 14 patients treated with the same regimen were considered. Articles were independently selected by at least two investigators. Fifty-five eligible articles were retrieved. Sixty% were dealing with platinum-based regimens, mainly cisplatin, and showed overall similar activity (mostly response rate above 50%) independently of the line of treatment or histological type (thymoma versus thymic carcinoma). Non-platinum based regimens included octreotide-prednisone and capecitabine-gemcitabine. Promising data of immunotherapy with antiPDL1 antibody (pembrolizumab) requires confirmation. Based on available data, the most popular and active regimens are cisplatin-anthracycline (CAP or ADOC) or cisplatin-etoposide combinations that should be recommended when considering first-line chemotherapy in thymoma or thymic carcinoma.

1. Introduction

On the basis of the RARE-CARE project definition [1], thymoma and thymic carcinoma are denominated rare cancers. Overall, the prognosis is good as a majority of patients are eligible for surgical resection of the tumour, possibly associated with adjuvant radiotherapy. Chemotherapy is reserved to patients with primarily non resectable tumours, with advanced stages (stages III-IV considering the Masaoka or the ITMIG classifications) in the setting of multimodal therapeutic strategies, and for recurrent or refractory disease.

So far, the question of the best chemotherapy regimen remains debatable. The rarity of the tumour precludes randomized trials to be conducted. The most frequent schedules include combination of platinum derivatives and anthracyclines while cisplatin-etoposide combinations are also popular. Some reviews have been published during the last decade [2–5]. However, some methodological concerns may be

☆ This study is supported by the EURACAN initiative. This is a production of the Laboratoire Facultaire de Médecine Factuelle de l'Université Libre de Bruxelles.
* Corresponding author at: Institut Jules Bordet, Rue Héger-Bordet, 1, B-1000, Brussels, Belgium.
E-mail address: thierry.berghmans@bordet.be (T. Berghmans).

https://doi.org/10.1016/j.lungcan.2018.10.018
Received 12 July 2018; Received in revised form 15 October 2018; Accepted 16 October 2018

Table 1
Summary of platinum-anthracycline-based studies.

Reference	N	CT regimen	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Loehrer 1994 [37]	30	CAP	29/1	16/14	77	50	MST 37.7 m; 2-year 64.5%	> 1	NO
Lee 1996 [38]	17	CAP	17/0	NR	NR	53	NR	1	NO
Kim 2004 [39]	22	CAP	10/12	9/13	91	77	5-year 95%	1	YES
Liu 2007 [8]	28	CAP	7/21	18/10	NR	71	NR	1	YES
Cardillo 2010 [9]	31	CAP	21/10	24/7	NR	58	NR	1	YES
Fornasiero 1991 [40]	37	ADOC	37/0	20/17	NR	92	NR	> 1	NO
Berruti 1993 [41]	6	ADOC	6/0	4/2	NR	83	NR	1	YES
Rea 1993 [42]	16	ADOC	16/0	8/8	NR	100	MST 66 m	1	YES
Berruti 1999 [43]	16	ADOC	16/0	9/7	94	81	MST 47.5 m	1	YES
Agatsuma 2011 [44]	34	ADOC	0/34	22/12	82	50	MST 21.3 m; 1-year 72.7%	1	NO
Rea F.s – 2011 [45]	38	ADOC	32/6	NR	NR	68	NR	1	YES
Oshita 1995 [10]	14	CAP-VP16	7/7	8/6	43	43	MST 14.7 m	1 and > 1	YES
Shin 1998 [46]	12	CAP-PDN	12/0	5/7	100	92	NR	NR	YES
Thomas 2014 [11]	26	CAP-belinostat	12/14	13/13	100	40	MST 28.5 m	> 1	NO
Yokoi 2007 [47]	14	CDDP-Dox-PDN	14/0	7/7	NR	93	NR	1	YES
Inoue 2014 [12]	51	CBDCA-amrubicin	18/33	25/26	100	25	NR	> 1	NO

N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; PDN = prednisone; CT = chemotherapy; Dox = doxorubicin; CDDP = cisplatin; CBDCA = carboplatin; CAP (cisplatin-adriamycin-cyclophosphamide); ADOC (cisplatin-doxorubicin-cyclophosphamide-vincristine).

raised: search equation not available, key-works not corresponding to MeSH words, or conventional terms used for literature search, leading to difficulties when trying to reproduce the literature selection. Other limitations are noted: study focused on a specific setting, English literature only, restricted temporal limits … Further, targeted therapies and immunotherapies are rapidly evolving therapeutics needing updated assessment.

The aim of this systematic review was to evaluate the effectiveness of the different systemic therapies, whatever the therapeutic line including chemotherapy, targeted therapies and immunotherapies in thymoma and thymic carcinoma, using the principles of evidence-based medicine. This study is a production of the Laboratoire Facultaire de Médecine Factuelle from the Université Libre de Bruxelles and is supported by the EURACAN initiative.

2. Material and methods

The primary objective of the systematic review was to assess the response rate of any systemic therapeutics in thymoma and thymic carcinoma, whatever the criteria used by the authors (WHO, RECIST …). Whatever setting of the disease, response rate is indeed a common endpoint and has the advantage of specifically assessing treatment efficacy in a disease for which survival is impacted by multimodal strategies and the possible delivery of multiple lines of systemic therapies. Secondary objectives are to assess overall survival, toxicity and response rate in selected subgroups of patients, defined on histology (thymoma vs thymic carcinoma), line of treatment, and stage.

The literature search was done in March 2018 using the Ovid Medline system. This research was performed by a scientific librarian (VD) experienced in searching for medical and scientific publications, and by a physician (TB) expert in the treatment of thoracic neoplasms and trained in evidence-based medicine.

Ovid Medline database was searched using the OvidSP interface. The “PICO” (population, intervention, comparator, outcome) model for clinical questions was used to identify the concepts included in the questions [6]. The corresponding search criteria of “P” and “I” were translated into MeSH terms, and free-text keywords that were searched for in titles, abstracts and name of substances (appendix 1). Citations were exported from Medline into a reference manager software to allow the removal of duplicates. All articles retrieved by the librarian were sent to at least two members of the group. They were first selected for their eligibility based on the abstract content and the language. Only publications accessible to the authors for their language (English, French, Dutch, German, Spanish, Italian) were deemed eligible. The final selection was made after reading the full publication. Selection was independently done by at least two members of the group and discrepancies were consensually resolved. This search was supplemented by screening the references of the selected articles and other literature known by the experts. A third investigator (NG) secondarily confirmed the final selection, independently.

The inclusion criteria were the following: phase II-III-IV or any other prospective studies (excluding phase I), retrospective study including at least 14 patients treated with the same chemotherapy regimen (adapted from Gehan’s schedule for phase II [7]), thymoma or thymic carcinoma histologically proven whatever the stage or the histological sub-type or the therapeutic line. If chemotherapy was included in a multimodality approach, response had to be assessable (adjuvant chemotherapy was not considered for the review). There was no selection based on year of publication.

The following parameters were expected to be retrieved from the publications: number of patients, main patients’ characteristics (performance status, gender), histological classification, staging system, targetable biological abnormalities, chemotherapy schedule, therapeutic line of chemotherapy (first vs further line), response rate (overall and for subgroups analyses based on histology and stage), survival, grade 3–4 toxicities (haematological versus non haematological).

3. Results

From an initial 3184 abstracts retrieved through the search equation, 434 potentially eligible studies were selected based on the content of the abstract and/or the title. Of whom, 55 were finally eligible for the systematic review (Flow chart in appendix 2).

Years of publication of eligible articles ranged from 1991 to 2018, with only 14 publications before 2000. Fourteen studies were retrospective in nature for 40 prospective non-randomized and one with an unclear status. Thirty-four studies were unicentric. The median number of patients was 20 (range 5–51). Authors used the following histological classification: Rosai and Levine or another similar classification (n = 5), WHO (n = 26), while it was not reported in 24 articles. Masaoka staging system was used in 38 studies and no definition was

Table 2
Summary of cisplatin-etoposide based studies.

Reference	N	CT regimen	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Giaccone 1996 [48]	16	CDDP-VP16	16/0	10/6	75	56	MST 4.3 years; 5-years 50%	> 1	NO
Mineo T. C.s – 2010	33	CDDP-VP16	33/0	20/13	NR	45	MST 30 m; 5-years 37%	1	YES
Tamiya 2014 [49]	5	CDDP-VP16	5/0	NR	100	40	MST 40.8m	NR	NO
Macchiarini 1991 [50]	20	CDDP-VP16-epirubicin	7/0	6/1	57	100	NR	1	YES
Venuta 1997 [51]	21	CDDP-VP16-epirubicin	21/0	NR	NR	100[a]	NR	1	YES
Lucchi 2005 [52]	36	CDDP-VP16-epirubicin	NR	NR	NR	66	NR	1	YES
Lucchi 2006 [53]	30	CDDP-VP16-epirubicin	30/0	13/17	NR	73	NR	1	YES
Hanna 2001 [54]	5	CBDCA-VP16 + autoBMT	4/1	4/1	100	100	NR	> 1	NO
Loehrer 2001 [13]	28	CDDP-VP16-IFO	20/8	17/11	86	32	MST 31.6 m; 1 and 2-years 89% and 70%	> 1	NO
Grassin 2010 [14]	16	CDDP-VP16-IFO	12/4	10/6	81	25	NR	1	NO
Kunitoh 2009 [55]	30	CDDP-VP16-Dox-VCR	30/0	16/14	97	59	MST 6.1 years; 2 and 5-years 89% and 65%	1	YES
Kunitoh 2010 [56]	23	CDDP-VP16-Dox-VCR	23/0	17/6	100	62	2 and 5-years 100% and 85%	1	YES

N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; CDP = cisplatin; CBDCA = carboplatin; autoBMT = autologous bone marrow transplantation; Dox = doxorubicin; VCR = vincristine; IFO = ifosfamide; VP16 = etoposide.

[a] no criteria defining response: "all patients showed radiologic evidence of tumor mass reduction" for stage II and "the metastases shrank in all patients" for stage IV; CT = chemotherapy.

provided in 17 cases.

The main type of chemotherapy was platinum-anthracycline-based without etoposide (n = 16, Table 1) followed by platinum-etoposide schedules (n = 12, Table 2) of whom 6 also contained anthracyclines, and platinum-taxanes regimens (n = 5, Table 3). Other treatments included conventional chemotherapies (n = 7, Table 4), targeted therapies (n = 7, Table 5), octreotide (n = 3, Table 5), epigenetic (n = 1, Table 4) or immunomodulatory agents (n = 4, Table 4). In 40 studies, some information regarding previous chemotherapy was provided: in 21, the tested regimen was the first given chemotherapy.

Comparative results for response rates according to the main chemotherapy regimens, in first-line and according to histology are presented in Fig. 1 a–d. Response rates (RR) for platinum-anthracyclines (without etoposide) based-regimens ranged from 25% (with carboplatin) to 100%. Adding etoposide to the combination did not add more activity, as RR ranged from 59% to 100%. The RR appeared similar for platinum-etoposide (without anthracyclines) regimens, ranging from 25% to 100%. On the opposite, platinum-taxanes combinations seemed less effective with RR between 30% and 63%. Most of these taxane combinations were proposed for relapsing tumours (exposed or not to previous chemotherapy regimens) and compared more to the results observed in the same setting for platinum-anthracyclines (without etoposide) (RR 25%–92%) and platinum-etoposide (without anthracyclines) (RR 32%–100%); they were also more given to thymic carcinomas, which are more aggressive. Patients treated with first-line chemotherapy, except two studies, showed RR largely above 50% (Tables 1–3). Most of these studies are used in a multimodal approach.

Based on RR, few other compounds mainly tested for salvage therapy, suggested high activity as combined octreotide-prednisone (RR 32–38% for salvage therapy but 88% front-line) or corticosteroids, ifosfamide, capecitabine-gemcitabine and S1 (Tables 4,5). Targeted therapies showed very limited activity (Table 5). A special emphasis should be settled for immunotherapy with a first trial testing pembrolizumab in relapsed thymic carcinoma. RR was only 22.5% but with prolonged duration of response leading to prolonged median OS (24.9 months).

We looked at the activity of chemotherapy separately in thymoma and thymic carcinoma. A definite conclusion seems difficult regarding the number of studies reporting this data and the limited number of patients. No systematic trend could be observed. Meanwhile, pathological review was not performed for a majority of studies. For platinum-anthracyclin, only five studies reported separate response rates (RR) between thymoma and thymic carcinoma: [8–12]. In 3 studies, RR was superior for thymoma ([8] 90% vs 61% [9], 62% vs 50% [11], 64% vs 21%) while in one study the opposite was observed ([12] 17% vs 30%). In the last study, the same RR was reported ([10] 43% in both histological types). Among the cisplatin-etoposide combinations, only two studies reported respective distinct RR. In the first study [13], a slight

Table 3
Summary of platinum-taxane-based studies.

Reference	N	CT regimen	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Furugen 2011 [57]	16	CBDCA-paclitaxel	0/16	13/3	94	38	MST 49.4 m	> 1	NO
Lemma 2011 [15]	44	CBDCA-paclitaxel	21/23	27/17	100	30	NR	> 1	NO
Hirai 2015 [58]	39	CBDCA-paclitaxel	0/39	23/16	100	36	1 and 2-year 85% and 71%	NR	NO
Park 2013 [16]	27	CDDP-docetaxel	9/18	16/11	NR	63	NR	1	YES
Kim 2015 [17]	42	CDDP-paclitaxel	14/28	30/12	100	63	NR	> 1	NO

N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; CDDP = cisplatin; Dox = doxorubicin; PDN = prednisone; CBDCA = carboplatin; CT = chemotherapy.

Table 4
Other drugs regimens.

Reference	N	CT regimen	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Bonomi 1993 [29]	21	CDDP	21/0	11/10	86	10	MST 76 w	> 1	NO
Highley 1999 [30]	17	IFO	15/2	9/8	NR	40	NR	1	NO
Palmieri 2014 [18]	30	Capecitabine-gemcitabine	22/8	18/12	90	40	MST 11 m	> 1	NO
Okuma 2016 [31]	14	S1	0/14	6/8	93	43	MST 30m 1-year 68.8%	> 1	NO
Bluthgen 2016 [19]	20	Etoposide	5/15	12/8	85	15	MST 41 m	> 1	NO
Liang 2015 [22]	16	Pemetrexed	6/10	11/5	69	13	MST 17.9 m	> 1	NO
Qian 2016 [21]	18	Pemetrexed	7/11	10/8	56	22	MST 32.7 m	> 1	NO
Gordon 1995 [59]	14	Rh-IL2	11/3	9/5	100	0	NR	> 1	NO
Kobayashi 2006 [60]	17	Corticosteroids	17/0	8/9	NR	47	NR	1	YES
Giaccone 2011 [20]	41	Belinostat	25/16	20/21	98	5	MST 19.2m 1 and 2-years 69% and 42%	> 1	NO
Giaccone 2018 [34]	40	Pembrolizumab	0/40	28/12	95	22.5	MST 24.9 m 1-year 71%	> 1	NO
Oji 2018 [33]	15	WT-1 peptide	4/11	10/5	NR	0	NR	> 1	NO

N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; CDDP = cisplatin; IFO = ifosfamide; CT = chemotherapy.

increased RR for thymoma was observed (35% vs 25%) while in the second [14], there was no difference but the limited number of patients precluded any definite conclusion (25% vs 25%). Three studies with cisplatin-taxanes reported some differential data between thymoma and thymic carcinoma. In one study [15], RR was better in thymoma (43% vs 22%) while in the two others [16,17], it was better in thymic carcinoma (56% vs 67% and 46% vs 70%). In five studies with other drugs, differential RR between thymoma and thymic carcinoma were reported. Etoposide [18] and the combination of capecitabine-gemcitabine [19] showed no difference according to histology (41% vs 37.5% and both 20%) while thymoma appears more sensitive to belinostat (8% vs 0%) [20] and to pemetrexed (43% vs 9%) [21] in one study but not in the other one (17% vs 10%) [22]. Targeted therapies reported very different data: Cixutumumab [23] showed better activity in thymoma (13.5% vs 0%), sunitinib demonstrated either a better activity in thymic carcinoma (6.3% vs 26%) [24] or a similar RR (28.6% vs 20%) [25] like everolimus (9.4% vs 16.7%) [26]. Finally, octreotide alone is also effective in both histologies (38.5% vs 33.3%) [27] but the association of octreotide and prednisone [28] showed better activity in thymoma (13.5% vs 0% and 37.5% vs 0%).

Survival rates are presented in Tables 1–5. It is difficult to perform a comparison of the different chemotherapy regimens. In numerous trials, these data were not reported. Further, there is major heterogeneity according to the therapeutic line or the integration of chemotherapy into a multimodal approach precluding any definite conclusions about the survival impact of chemotherapy outside of a randomized comparative trial. These results are presented essentially in an informative way.

Expecting a comparison between the main platinum-based combinations, we looked at the 3 main grades 3–4 expected toxicities of cisplatin: neutropenia, thrombopenia and renal failure. In 33 studies, there was no information regarding these 3 variables in 19, 15, and 13 publications, respectively. No grade 3–4 renal toxicity was reported whatever the platinum regimen. Grade 3–4 neutropenia and thrombopenia were reported in 27–100% and 0–46% for cisplatin-anthracyclines without etoposide (82% and 20% for carboplatin-amrubicin), 61–87% and 27–46% for cisplatin-anthracyclines with etoposide, 18% and 0–44% for cisplatin-etoposide (100% both for carboplatin-etoposide with autologous bone marrow transplant), 10–30% and 0–4% for cisplatin-taxanes, 24–87% and 0–5% for carboplatin-taxanes. Due to the limited information, it is not meaningful concluding to a clinically significant differential haematological toxicity. For other drugs, no specific signal could be derived from the publications (data not show) except for pembrolizumab where immune toxicity was reported but at

Table 5
Summary of targeted therapies and octreotide.

Reference	N	Drugs	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Giaccone 2009 [61]	7	Imatinib	2/5	6/1	43	0	MST 4 m	> 1	NO
Palmieri 2012 [62]	15	Imatimib	12/3	10/5	100	0	NR	> 1	YES
Rajan 2014 [23]	49	Cixutumumab	37/12	26/23	84	10	MST 16.2m 5-year 0%	> 1	NO
Thomas 2015 [24]	40	Sunitinib	16/24	22/18	90	32	NR	> 1	NO
Remon 2016 [25]	28	Sunitinib	8/20	19/9	89	22	MST 15.4 m	> 1	NO
Gubens 2015 [63]	21	Saracatinib	12/9	11/10	NR	0	MST 23.1 m	> 1	NO
Zucali 2018 [26]	50	Everolimus	32/18	28/22	100	12	MST 25.7 m 1-year 72%	> 1	NO
Palmieri 2002 [27]	16	Octreotide + PDN	13/3	8/8	NR	38	MST 15 m	> 1	NO
Loehrer 2004 [28]	38	Octreotide +/- PDN	32/6	19/19	100	32	1 and 2-years 87% and 76%	> 1	NO
Kirzinger 2016 [64]	17	Octreotide + PDN	15/2	4/13	94	88	NR	1	NO

N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; PDN = prednisone; CT = chemotherapy.

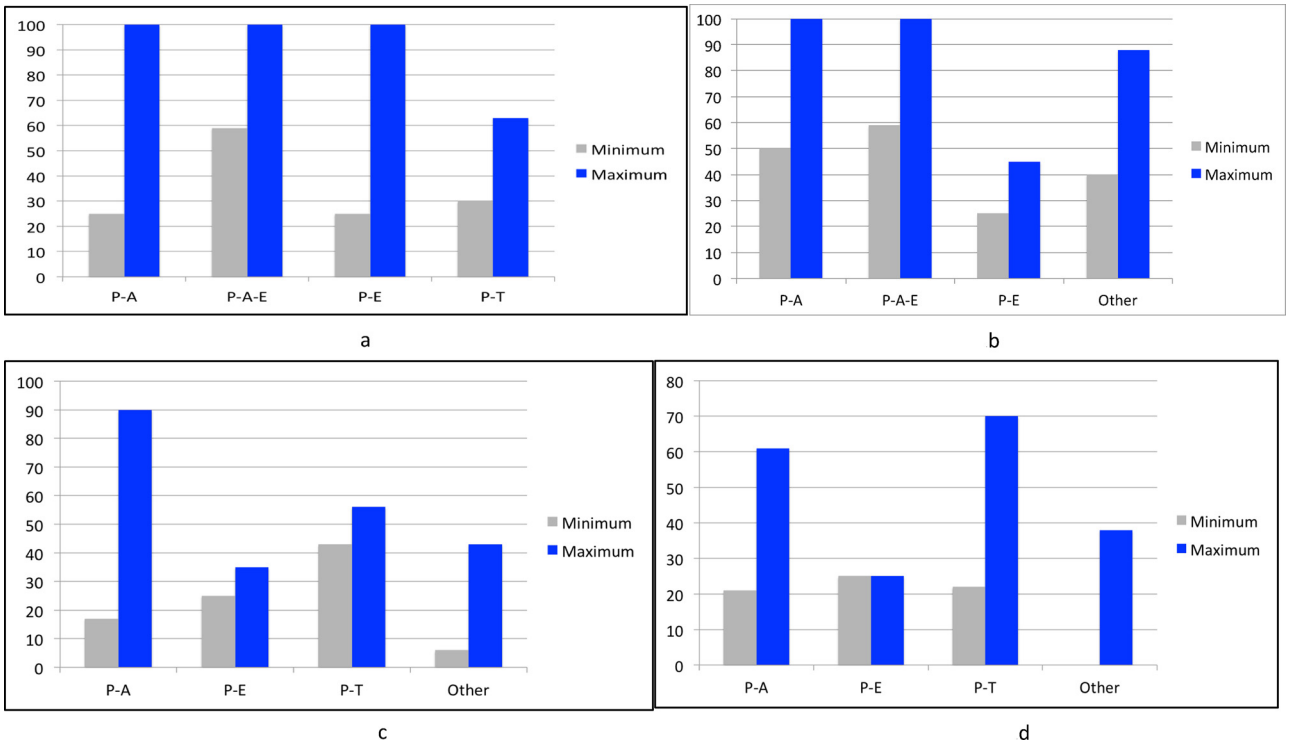

Fig. 1. (a) Response rates of platinum-based regimens. (b) Response rates of 1st line therapy. (c) Response rates in thymoma. (d) response rates in thymic carcinoma.

similar level than in lung cancer.

A lot of expected information (see parameters to be retrieved in the material and methods section) was not available or too partially reported in the publications, precluding any meaningful conclusion or comparisons. For this reason, we do not present data on activity according to stage; this information was provided in 43 studies and in 36, only stages III-IV were considered while for the last 7 studies, the percentage of stage III-IV ranged from 25% to 94%.

4. Discussion

This large systematic review is presenting updated data on clinical activity of chemotherapy in thymoma and thymic carcinoma. The most popular regimens include platinum derivatives, mainly cisplatin with anthracyclines and/or etoposide, showing response rates above 50% in most of the series, whatever in front-line as for neoadjuvant therapy or in case of relapsing tumours. These regimens appear having a similar activity in thymoma and thymic carcinoma. A few other conventional drugs showed interesting activity while targeted therapies are poorly active or ineffective. Immunomodulatory agents demonstrated promising activity signals needing confirmation.

While chemotherapy is less frequently used in thymic tumours than for other thoracic cancers, mainly because of a disease extent allowing complete surgical resection possibly followed by adjuvant radiotherapy, systemic therapy is needed for locally advanced/ metastatic or relapsing tumours, alone or in a multimodality approach. Most of the retrospective series and prospective studies include a limited number of patients, justifying a more comprehensive approach by a systematic review. Thymomas are known to be more sensitive to chemotherapy, what may partly be related to a “lympholytic effect” of cytotoxic agents and steroids in type B thymomas; meanwhile, thymic carcinomas which are more frequently refractory to chemotherapy, usually present with metastatic disease upfront, leading to deliver exclusive chemotherapy with no intent of subsequent focal treatment.

Based on our data, a cisplatin-based regimen should be proposed for first-line therapy, whatever considering as a (neo)adjuvant treatment or for extensive disease, independently of histology (thymoma or thymic carcinoma). We may question about the best cisplatin-based regimen. Cisplatin-anthracyclines (without etoposide) showed similar range of RR than cisplatin-etoposide, survival being difficult to interpret considering the limited reported data and the number of multimodal approaches. Combining etoposide to cisplatin-anthracycline does not seem to add supplemental activity. Toxicity profiles appear also similar, except for cardiac toxicity expected with anthracycline that should be used with caution when considering radiotherapy in the therapeutic plan. Carboplatin-paclitaxel may be an interesting schedule due to its easy use while it was mainly tested for salvage therapy and in the setting of thymic carcinoma. Based on our data, it is not possible recommending with a high-evidence level its use as front-line therapy but proposing it more for salvage therapy. Due to a lack of data, it was not possible to evaluate replacing cisplatin by carboplatin in fit patients, both drugs having different toxicity profiles.

For second and upper lines, taxanes-based combination seems appropriate. Non-platinum-based chemotherapy consisted mainly in single conventional agent [19,21,29–31] with relatively low response rates but, at the difference of combined regimens, they were quite always used for salvage therapy, expecting the tumours to be more resistant to chemotherapy. Meanwhile, clinicians’ expectation may be stable disease in the setting of refractory tumors, what may have some value as tumor growth may be slow, especially in thymomas. According to response rates, capecitabine-gemcitabine, S1 (a prodrug of 5-Fluorouracil inhibiting the Dihydropyrimidine Dehydrogenase) or octreotide-prednisone seems promising alternatives.

Immunotherapy is currently a revolution in different epithelial tumour types, as for non-small cell lung cancer [32], essentially with antiPD1/PDL-1 antibodies. Outside of corticosteroids that have a specific mode of action through a lympholytic effect in thymomas, and were mainly added to chemotherapy and octreotide, three other single agent immunomodulatory agents have been reported so far. Epigenetic modulation by a histone deacetylase inhibitor (belinostat) [20] and an immune system antigen-stimulating peptide [33] did not show encouraging results. However, second-line pembrolizumab [34], an

antiPDL-1 antibody, demonstrated promising RR and especially survival in thymic carcinoma. As expected due to frequent auto-immune paraneoplastic syndrome observed in thymic tumours, immune toxicity was a concern with few grade 4 events but potentially life-threatening. Those immune-related adverse events, well known in lung cancer are retrieved in thymic tumours (dysthyroidism, hepatitis, rash) but major signals of less recognised toxicity were observed with severe grade 4 myocarditis and grade 3 myositis. A second unpublished recently reported study on 15 patients with thymoma [35] showed limited activity of nivolumab in this setting, at least in terms of early response and PFS. Further studies are needed and the EORTC is now opening a two-step phase II study assessing second-line nivolumab in B3 thymoma and thymic carcinoma (NIVOTHYM NCT03134118).

This literature systematic review has some limitations. It was not possible to perform a quantitative data aggregation as heterogeneity in the design of the selected publications was too important: line of treatment, integration or not of chemotherapy into a multimodal approach, different repartition of histological subtypes. Also, this heterogeneity did not allow performing subgroup analyses according to histological thymoma subtypes and stage. For this latter, most of the studies were dealing with advanced diseases (stages III-IV according to the Masaoka staging system) or relapsing tumours so that our data could be safely used in this clinical setting. The design of our review was quite different from previous published systematic reviews. We designed a comprehensive search equation by both an experienced librarian and clinicians' experts in thoracic oncology. This approach has yet been experimented with success in lung cancer [36].

5. Conclusions

Based on available data, the most popular and active regimens are cisplatin-anthracycline (CAP or ADOC) or cisplatin-etoposide combinations that should be recommended when considering first-line chemotherapy in thymoma or thymic carcinoma. Other platinum combinations with taxanes seem adequate alternatives, mainly in second-line setting or for thymic carcinomas. Immunotherapy with antiPD1/PDL-1 or other antibodies showed early promising data that need further confirmation, with special emphasis on immune-related toxicity. Registering patients with thymic tumours in clinical trials and prospective registries based on recommendations to build cohorts of patients treated according to similar algorithms is of particular importance if we aim improving scientific knowledge and prognosis of this rare tumour.

Conflict of interest

Nicolas Girard discloses the following conflict of interest: BMS: clinical research, consultancy, MSD: clinical research, consultancy, Pfizer: clinical research, consultancy

The other authors have no conflict of interest in relationship with the content of the manuscript to be disclosed.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.10.018.

References

[1] S. Siesling, J.M. van der Zwan, I. Izarzugaza, et al., Rare thoracic cancers, including peritoneum mesothelioma, Eur. J. Cancer 48 (2012) 949–960.

[2] F. Hirai, R. Toyozawa, K. Nosaki, T. Seto, Are anthracycline-based regimens truly indicated to be the standard chemotherapy regimen for thymic carcinoma? J. Thoracic Oncol. 11 (2016) 115–121.

[3] Y. Okuma, M. Saito, Y. Hosomi, et al., Key components of chemotherapy for thymic malignancies: a systematic review and pooled analysis for anthracycline-, carboplatin- or cisplatin-based chemotherapy, J. Cancer Res. Clin. Oncol. 141 (2015) 323–331.

[4] R. Berardi, M. De Lisa, S. Pagliaretta, et al., Thymic neoplasms: an update on the use of chemotherapy and new targeted therapies. A literature review, Cancer Treat. Rev. 40 (2014) 495–506.

[5] C.B. Falkson, A. Bezjak, G. Darling, et al., The management of thymoma: a systematic review and practice guideline, J. Thoracic Oncol. 4 (2009) 911–919.

[6] D.L. Sackett, Evidence-based Medicine: How to Practice and Teach EBM, Churchill Livingstone, New York; Edinburgh, 2000.

[7] E.A. Gehan, The determinatio of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent, J. Chronic Dis. 13 (1961) 346–353.

[8] J.M. Liu, L.S. Wang, M.H. Huang, et al., Topoisomerase 2alpha plays a pivotal role in the tumor biology of stage IV thymic neoplasia, Cancer 109 (2007) 502–509.

[9] G. Cardillo, F. Carleo, R. Giunti, et al., Predictors of survival in patients with locally advanced thymoma and thymic carcinoma (Masaoka stages III and IVa), Eur. J. Cardio-thoracic Surg. 37 (2010) 819–823.

[10] F. Oshita, T. Kasai, T. Kurata, et al., Intensive chemotherapy with cisplatin, doxorubicin, cyclophosphamide, etoposide and granulocyte colony-stimulating factor for advanced thymoma or thymic cancer: preliminary results, Jpn. J. Clin. Oncol. 25 (1995) 208–212.

[11] A. Thomas, A. Rajan, E. Szabo, et al., A phase I/II trial of belinostat in combination with cisplatin, doxorubicin, and cyclophosphamide in thymic epithelial tumors: a clinical and translational study, Clin. Cancer Res. 20 (2014) 5392–5402.

[12] A. Inoue, S. Sugawara, M. Harada, et al., Phase II study of Amrubicin combined with carboplatin for thymic carcinoma and invasive thymoma: north Japan Lung Cancer group study 0803, J. Thoracic Oncol. 9 (2014) 1805–1809.

[13] P.J. Loehrer, Sr, M. Jiroutek, S. Aisner, et al., Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial, Cancer 91 (2001) 2010–2015.

[14] F. Grassin, N. Paleiron, M. Andre, et al., Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma. A French experience, J. Thoracic Oncol. 5 (2010) 893–897.

[15] G.L. Lemma, J.W. Lee, S.C. Aisner, et al., Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma, J. Clin. Oncol. 29 (2011) 2060–2065.

[16] S. Park, M.J. Ahn, J.S. Ahn, et al., A prospective phase II trial of induction chemotherapy with docetaxel/cisplatin for Masaoka stage III/IV thymic epithelial tumors, J. Thoracic Oncol. 8 (2013) 959–966.

[17] H.S. Kim, J.Y. Lee, S.H. Lim, et al., A Prospective Phase II Study of Cisplatin and Cremophor EL-Free Paclitaxel (Genexol-PM) in Patients with Unresectable Thymic Epithelial Tumors, J. Thoracic Oncol. 10 (2015) 1800–1806.

[18] G. Palmieri, C. Buonerba, M. Ottaviano, et al., Capecitabine plus gemcitabine in thymic epithelial tumors: final analysis of a Phase II trial, Future Oncol. 10 (2014) 2141–2147.

[19] M.V. Bluthgen, C. Boutros, F. Fayard, et al., Activity and safety of oral etoposide in pretreated patients with metastatic or recurrent thymic epithelial tumors (TET): a single-institution experience, Lung Cancer 99 (2016) 111–116.

[20] G. Giaccone, A. Rajan, A. Berman, et al., Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors, J. Clin. Oncol. 29 (2011) 2052–2059.

[21] X. Qian, Z. Song, Efficacy of pemetrexed-based regimen in relapsed advanced thymic epithelial tumors and its association with thymidylate synthetase level, Onco. Ther. 9 (2016) 4527–4531.

[22] Y. Liang, S.K. Padda, J.W. Riess, et al., Pemetrexed in patients with thymic malignancies previously treated with chemotherapy, Lung Cancer 87 (2015) 34–38.

[23] A. Rajan, C.A. Carter, A. Berman, et al., Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: a multicentre, open-label, phase 2 trial, Lancet Oncol. 15 (2014) 191–200.

[24] A. Thomas, A. Rajan, A. Berman, et al., Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial.[Erratum appears in Lancet Oncol. 2015 Mar;16(3):e105; PMID: 25752557], Lancet Oncol. 16 (2015) 177–186.

[25] J. Remon, N. Girard, J. Mazieres, et al., Sunitinib in patients with advanced thymic malignancies: cohort from the French RYTHMIC network, Lung Cancer 97 (2016) 99–104.

[26] P.A. Zucali, T. De Pas, G. Palmieri, et al., Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy, J. Clin. Oncol. 36 (2018) 342–349.

[27] G. Palmieri, L. Montella, A. Martignetti, et al., Somatostatin analogs and prednisone in advanced refractory thymic tumors, Cancer 94 (2002) 1414–1420.

[28] P.J. Loehrer, Sr, W. Wang, D.H. Johnson, et al., Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: an Eastern Cooperative Oncology Group Phase II Trial. [Erratum appears in J Clin Oncol. 2004 Jun 1;22(11):2261], J. Clin. Oncol. (22) (2004) 293–299.

[29] P.D. Bonomi, D. Finkelstein, S. Aisner, D. Ettinger, EST 2582 phase II trial of cisplatin in metastatic or recurrent thymoma, Am. J. Clin. Oncol. 16 (1993) 342–345.

[30] M.S. Highley, C.R. Underhill, F.X. Parnis, et al., Treatment of invasive thymoma with single-agent ifosfamide, J. Clin. Oncol. 17 (1999) 2737–2744.

[31] Y. Okuma, Y. Hosomi, S. Miyamoto, et al., Correlation between S-1 treatment outcome and expression of biomarkers for refractory thymic carcinoma.[Erratum appears in BMC Cancer. 2016;16(1):272; PMID: 27084341], BMC Cancer 16 (2016) 156.

[32] T. Berghmans, B. Grigoriu, J.P. Sculier, A.P. Meert, [Immune checkpoint inhibitors (antibodies to PD1 and PD-L1), a new therapeutic weapon against non-small cell bronchial carcinoma], Rev. Mal. Respir. 35 (2018) 197–205.

[33] Y. Oji, M. Inoue, Y. Takeda, et al., WT1 peptide-based immunotherapy for advanced thymic epithelial malignancies, Int. J. Cancer (2018) 11.

[34] G. Giaccone, C. Kim, J. Thompson, et al., Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study, Lancet Oncol. 19 (2018) 347–355.
[35] T. Seto, Y. Katsuya, H. Horinouchi, et al., 112O Primary result of an investigator-initiated phase II trial of nivolumab for unresectable or recurrent thymic carcinoma: PRIMER study (NCCH1505), J. Thorac. Oncol. 13 (2018) S61–S62.
[36] V. Durieux, M. Coureau, A.P. Meert, et al., Autoimmune paraneoplastic syndromes associated to lung cancer: a systematic review of the literature, Lung Cancer 106 (2017) 102–109.