Systemic treatments for thymoma and thymic carcinoma: a systematic review.

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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.

Key-words: thymoma, thymic carcinoma, chemotherapy, systematic review

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 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.

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).

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 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 figures 1a-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 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 to 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 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%.

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].

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.

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

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