General Thoracic and Cardiovascular Surgery (2019) 67:524–529
https://doi.org/10.1007/s11748-018-01054-7

ORIGINAL ARTICLE

Multimodality therapy for thymoma patients with pleural dissemination

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Received: 27 August 2018 / Accepted: 17 December 2018 / Published online: 6 February 2019

Abstract

Background Although multidisciplinary treatment is recommended for patients with advanced stage and recurrent thymoma, a detailed treatment strategy remains controversial. We have performed a multimodality therapy of induction chemotherapy (CAMP therapy: cisplatin, doxorubicin, and methylprednisolone) combined with surgery for those patients. We now conducted a retrospective study for investigating the results of this multimodality therapy for thymoma patients with pleural dissemination.

Patients and methods Between 2003 and 2017, 201 patients underwent surgical resection for thymomas. Twenty-six of them received induction CAMP therapy followed by surgery, and 19 of them with pleural dissemination were enrolled in this study. Those cohort were divided into 2 groups by employing surgical procedures: extrapleural pneumonectomy (EPP) group ($n = 10$) and resection of plural dissemination (RPD) group ($n = 9$).

Results The median age of all patients was 49 years. Based on the WHO classification, the histological diagnoses of those thymomas were as follows: Type B1 ($n = 1$), Type B2 ($n = 13$), and Type B3 ($n = 5$). Seven patients were complicated with myasthenia gravis (MG). Clinical stage of the 13 primary cases based on the Masaoka classification were stage IV, and the remaining six cases had recurrent pleural dissemination after surgery. Partial response in induction CAMP therapy was obtained in 78.9% ($n = 15$) of the patients. Adverse events (Grade 4) occurred in 2 patients (10.5%). Postoperative complications (Grade 4) were observed in 2 patients (10.5%). In all of the enrolled patients, the five-year overall survival rate (5Y-OS) and 5-year progression-free survival rate (5Y-PFS) were 76.7% and 55.1%, respectively. In the EPP group, 5Y-OS and 5Y-PFS were 83.3% and 83.3%, respectively, and in the RPD group, 70.0% and 29.6%, respectively.

Conclusions Multidisciplinary treatment using induction CAMP therapy and surgical resection for thymoma patients with pleural dissemination was effective and feasible. Because of the low recurrent rate of disease, young patients with good cardiopulmonary function and well-controlled MG might be good candidates for EPP.

Keywords Thymic malignancy · Thymoma · Multidisciplinary treatment · Pleural dissemination · Induction chemotherapy

Introduction

Thymoma is a thymic neoplasm that grows relatively slowly and generally responds to surgical resection, chemotherapy and radiotherapy [1]. For patients with stage I and II thymoma, primary resection is recommended. On the other hand, multidisciplinary treatment is required for patients with advanced stage and recurrent thymoma [2]. However, detailed treatment strategies including chemotherapy regimen and optimal surgical procedures remain controversial.

Patients with thymoma are often complicated with associated diseases such as myasthenia gravis (MG), pure red cell aplasia, hypo-gammaglobulinemia and so on [3]. Therefore,

This work was presented at the 70th Annual Scientific Meeting of The Japanese Association for Thoracic Surgery.

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although it is considered that radical resection is needed for advanced stage and recurrent thymoma to achieve R0 resection, sometimes it could not be acceptable to choose radical resection but palliative resection. Surgeons must choose a well-balanced surgical treatment for those complicated patients.

We have performed a multimodality therapy including induction chemotherapy (CAMP therapy: cisplatin, doxorubicin, and methylprednisolone) combined with surgery for patients with advanced stage and recurrent thymoma [4, 5]. We now conducted a retrospective study for investigating the results of the multimodality therapy for thymoma patients with pleural dissemination, including patients complicated with MG.

Patients and methods

Between 2003 and 2017, two hundred and one consecutive patients with thymoma underwent surgical resection at Nagoya University Hospital. Twenty-six of them received induction chemotherapy followed by surgery, and 19 among them with pleural dissemination were enrolled in the current study. All information on radiological and pathological variables was collected from the medical records. This retrospective study protocol was approved by the institutional review boards of the university hospital. Pathological staging was based on the Masaoka staging system [6], and histological classification was according to the World Health Organization (WHO) classification [7].

Therapeutic strategy

The chemotherapy regimen consisted of cisplatin (20 mg/m^2 per day, continuous infusion on days 1 through 4), doxorubicin (40 mg/m^2 intravenously on day 1), and methylprednisolone (1000 mg/day intravenously on days 1 through 4 and 500 mg/day intravenously on days 5 and 6) (CAMP therapy) [5]. Treatment cycles were repeated every 21–28 days. Surgical resection was attempted after three or four cycles of the chemotherapy. Our concepts of surgical procedures for those patients after induction chemotherapy were as follows; for selected young patients whose cardiopulmonary function was sufficient to undergo pneumonectomy, a thymectomy combined with extrapleural pneumonectomy (EPP) was performed. The stress electrocardiogram, echocardiography, pulmonary functional test and pulmonary perfusion scintigraphy of the patients were examined for investigating whether pneumonectomy was tolerable. When it was concluded that a patient could tolerate pneumonectomy, it was also thought that the patient could tolerate EPP. For patients complicated with MG, when their general condition was stable with/without low dose of steroid and/or pyridostigmine, we considered that the patients were also acceptable for receiving EPP. None of the patients were treated with immunosuppressive agents prior to EPP. The age limit for performing EPP was under 70 years. For patients whose general and/or disease condition was not indicated for EPP, a thymectomy and resection of the visible disseminated nodules in the pleural cavity were performed. Those 19 patients were divided into 2 groups by the surgical procedures employed: EPP with or without thymectomy (EPP) group ($n=10$), and resection of plural disseminated nodules with or without thymectomy (RPD) group ($n=9$).

Follow-up and evaluation

The patients were followed up every 1–3 months for 2 years after completion of the multimodality therapy and every 6 months thereafter. All patients were followed up until August 2018, and the median follow-up period for surviving patients was 59.7 months (16.1–184.2 months). The patients were evaluated with computed tomography (CT) and positron emission tomography (PET)/CT before and after induction chemotherapy. Response to induction chemotherapy was evaluated according to RECIST criteria [8]. Adverse events associated with chemotherapy and surgical treatments were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Statistical analysis

Overall survival was measured from the first day of treatment at our hospital for advanced and recurrent thymoma until death from any cause or the last date of follow-up. Progression-free survival was measured from the first day of treatment until progression of disease or death from any cause or the last date of follow-up. Overall and progression-free survival curves were calculated by the Kaplan–Meier estimation method using a log-rank test. All statistical analyses were performed with R 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The patients' characteristics are summarized in Table 1. Seven of the 19 patients were complicated with MG. The clinical stage of the 13 primary cases was IV, and the remaining six were recurrent cases of pleural disseminations after surgical treatment. Half of the patients received 4 courses or more of induction CAMP therapy. Responses for CAMP chemotherapy were as follows: PR ($n=15$; 78.9%) and SD ($n=4$; 21.1%) (Fig. 1). Adverse events (Grade 3 and 4) by CAMP therapy occurred in 10 patients (Table 2).

Table 1 Patient characteristics

Characteristic	All patients ($n=19$)	EPP group ($n=10$)	RPD group ($n=9$)
Age, years (median) (range)	49 (32–70)	49 (32–60)	52 (42–70)
Sex			
Male	11	4	7
Female	8	6	2
Associated disease			
MG	7	2 (under control)	5
None	12	8	4
Histology (WHO classification)			
B1	1	1	
B2	13	6	7
B3	5	3	2
Disease status			
Primary	13	8	5
Recurrent	6	2	4
Number of courses of performed chemotherapy			
1 course	4	2	2
2 courses	1	1	
3 courses	5	2	3
4 courses or more	9	5	4
Response for CAMP therapy			
PR	15	7	8
SD	4	3	1

EPP extrapleural pneumonectomy, *RPD* resection of pleural dissemination, *MG* myasthenia gravis, *CAMP therapy* regimen consisting of cisplatin, doxorubicin, and methylprednisolone

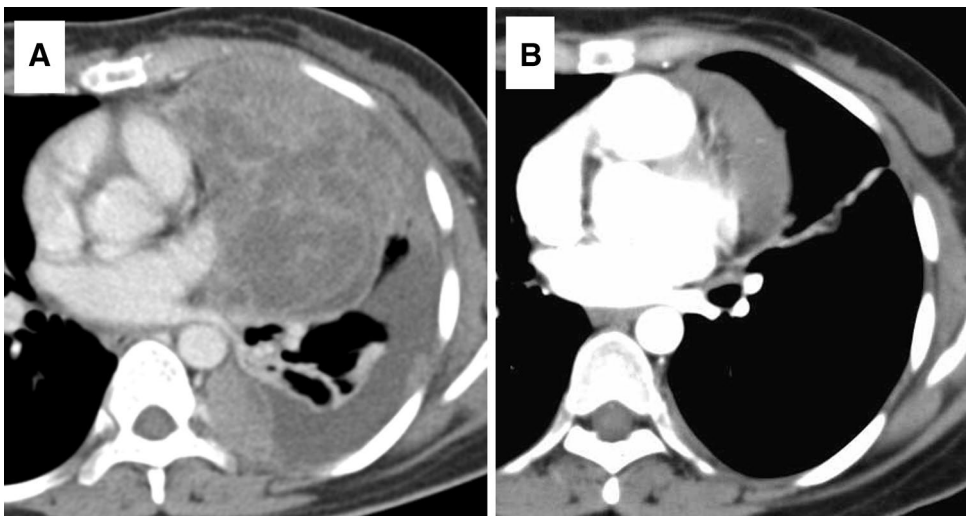

Fig. 1 **a** Chest computed tomography shows primary thymic mass and pleural nodules in the left thoracic cavity in a 32-year-old female before treatment. **b** Chest computed tomography shows the left thoracic cavity after induction CAMP therapy. The primary thymic mass and pleural nodules were dramatically reduced. Thereafter, she received thymectomy combined with extrapleural pneumonectomy (EPP), and the tumor histology was B2 thymoma. The patient is now alive with disease 65 months after EPP, and chest wall recurrence was under control with radiotherapy

Table 2 Toxicities by induction CAMP chemotherapy

Events	Grade 3	Grade 4	% of patients with toxicities ≥ G3
Neutropenia	4	1	26.3
Pneumonia	1	1	10.5
Dehydration	2	–	10.5
Nausea	1	–	5.3
Varicella zoster	1	–	5.3

Table 3 Postoperative complications

Events	Grade 3	Grade 4	% of patients with adverse events ≥ G3
Bleeding	–	1 (EPP)	5.3
Heart failure	–	1 (EPP)	5.3
MG crisis	1 (RPD)	–	5.3
Paralytic ileus	1 (RPD)	–	5.3
Massive pleural effusion	1 (RPD)	–	5.3

One RPD patient had 2 complications: MG crisis and paralytic ileus

MG myasthenia gravis, *RPD* resection of pleural dissemination group, *EPP* extrapleural pneumonectomy group

Postoperative complications (G3 and G4) were observed in 4 patients (Table 3).

In all of the enrolled patients, 5-year (5Y-OS) and 10-year (10Y-OS) overall survival rates were both 76.7% (Fig. 2a), and 5-year (5Y-PFS) and 10-year (10Y-PFS) progression-free survival rates were 55.1% and 45.9%, respectively. In the EPP group, the 5Y- and 10Y-OS rates were both 83.3% (Fig. 2c), and 5Y- and 10Y-PFS rates were both 83.3% (Fig. 2d). In the EPP group, one patient died from respiratory failure without recurrence 53 months after surgery. In the RPD group, 5Y- and 10Y-OS rates were both 70.0%, and 5Y- and 10Y-PFS rates were 29.6% and 14.8%, respectively (Fig. 2f). In the RPD group, the OS rate was high despite the low PFS rate. All the recurrent sites were the pleural cavity. Table 4 shows a summary of the recurrent patients in the RPD group, which indicated that customized and suitable treatments were performed for each patient with steroid therapy and/or radiation therapy.

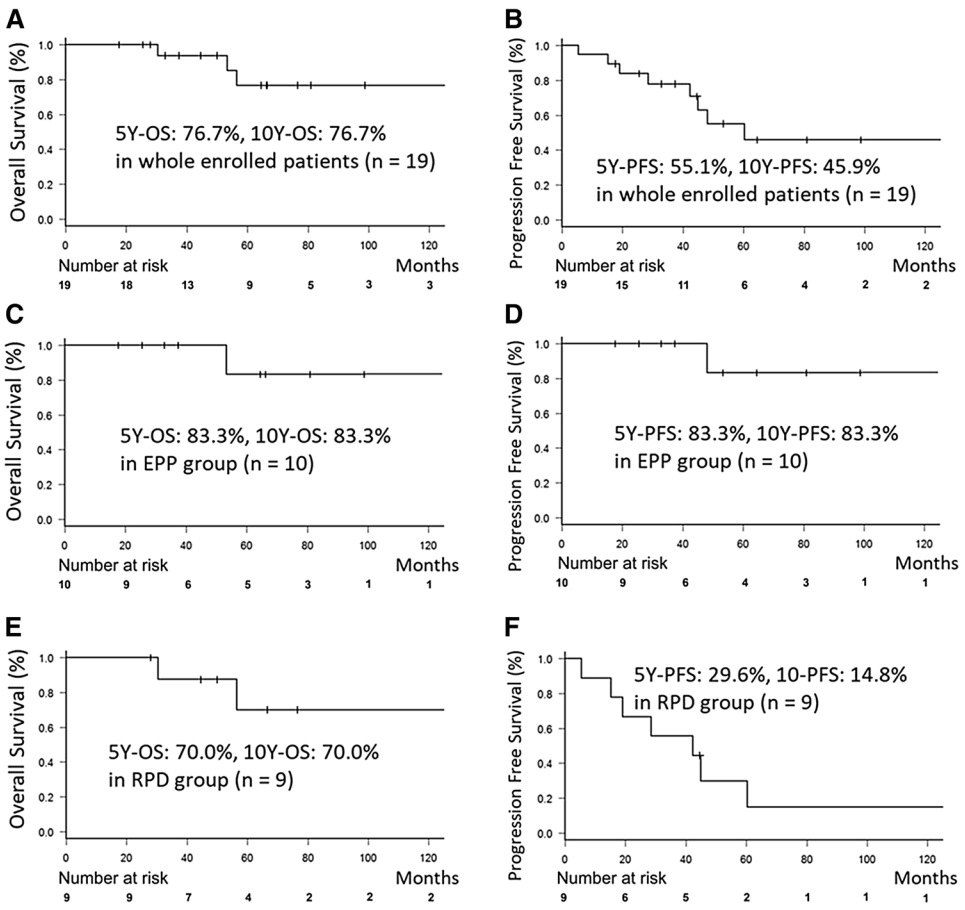

Fig. 2 **a, b** Overall survival and progression-free survival curves of all the enrolled patients. **c, d** Overall survival and progression-free survival curves of patients who received an extrapleural pneumonectomy after induction CAMP therapy. **e, f** Overall survival and progression-free survival curves of patients who received a resection of the disseminated pleural nodules after induction CAMP therapy

Table 4 Summary of recurrent patients in the RPD group ($n=7$)

Cases	Associated disease	Recurrent site	Treatment after recurrence	Survival (months)	Status
1	MG	Pleura	RT × 2 times	28	AWD
2	–	Pleura	Re-RPD	50	AWD
3	–	Pleura	PSL	67	AWD
4	MG	Pleura	PSL + TAC	77	AWD
5	MG	Pleura	RT × 5 times	179	AWD
6	MG	Pleura	RT × 2 times + steroid pulse therapy	31	DOD
7	–	Pleura	Observation	56	DOD

Steroid therapy was initially used mainly for MG, not recurrent tumors. As a result, steroids often served as a disease suppressor

RPD resection of pleural dissemination, *MG* myathsenia gravis, *RT* radiation therapy, *PSL* prednisolone, *TAC* tacrolimus, *AWD* alive with disease, *DOD* dead of disease

Discussion

For patients with early stage thymoma, surgical resection is considered the mainstay of therapy; nevertheless, the standard treatment strategy for advanced stage and recurrent thymoma patients has not been established. Because complete resection of those advanced thymoma was occasionally difficult to achieve, various trials of treatment strategy have been enforced. Thereafter, multimodality therapy with induction chemotherapy followed by surgical resection is nowadays widely accepted as a feasible treatment strategy and is considered to promise long-term survival [4, 9].

The reasons why multidisciplinary treatment using induction chemotherapy is needed for patients with advanced stage and recurrent thymoma including those complicated with pleural dissemination are considered as follows: for increasing macroscopic complete resection rates, gaining safety surgical margin by tumor regression, controlling pleural and pericardial dissemination, and scarring of tumors.

Although no standard combination chemotherapy for thymomas has been established, several regimens have been introduced [5, 10–12]. Yokoi et al. reported their experience of chemotherapy for patients with advanced stage thymomas [5]. The regimen consisted of cisplatin, doxorubicin, and methylprednisolone called CAMP. The response rate was 92.9%, the 5- and 10-year overall survival rates were both 80.7%, and the major adverse event associated with CAMP therapy was only acceptable neutropenia. They concluded that CAMP therapy was highly effective for advanced stage thymomas, and that multidisciplinary therapy including this chemotherapy was justifiable for the initial treatment of patients with advanced stage and recurrent thymoma. Our current study also used this regimen prior to surgery and showed the feasibility and safety of this multidisciplinary treatment.

Hence, macroscopic complete resection of the tumors might provide a promising good prognosis in stage IVa thymomas [3, 13, 14]. We considered that EPP was an ideal approach in selected relatively young patients with adequate cardiopulmonary function and well-managed MG by medications when complicated. The induction CAMP therapy might assist the EPP procedure to achieve complete resection, and OS and PFS rates were excellent in the EPP group as evident from the results of this study. Actually, several patients who received the same treatment strategy were reported to have long disease-free survival over 20 years [5]. We believe that complete resection after induction CAMP therapy was one of the effective treatment strategies for young thymoma patients with pleural dissemination. It has been reported that the number of disseminated nodules is one of the prognostic factors for thymoma patients [15]. In the current study, almost all patients had over ten pleural nodules, and it was difficult to count the correct number of nodules. We considered that patients with several nodules were suitable for RPD and the other patients were indicated for EPP.

On the other hand, some patients with pleural disseminations were not indicated for radical resection of EPP because of aging, insufficient cardiopulmonary conditions, and/or complications (e.g., MG, hypo-gammaglobulinemia, and pure red cell aplasia). For those patients, we performed induction CAMP therapy followed by resection of visible pleural nodules, and as a result the PFS rate was low despite the high OS rate. This reason was that customized and suitable therapy might be performed after recurrence of disease for each case with steroid therapy, radiation therapy, and/or surgical resection. In other words, they were forced to receive some repeated treatments after recurrences, resulting in their long-term prognoses. Those recurrent diseases progress gradually, but finally patients die of disease or deterioration of the general condition because of loss of tolerance for any treatment. In Table 4, all recurrent patients except one in the RPD group did not receive surgical treatment. Although we suppose that surgical treatment is effective for RPD recurrent patients, in this series there were a few tolerable cases for repetitive surgical treatments. We consider

that recurrent patients without tolerability for surgery are indicative for re-CAMP or radiation therapy.

Among the total enrolled patients of the current study, the OS rates were almost equivalent in comparison with previous studies [15–17]. However, the PFS rate in our EPP group was as high as the OS rate, while in the RPD group the OS rate was also high but the PFS rate was very low. There were very few reports of PFS rates after multidisciplinary treatments for advanced stage thymoma, and our results could not be compared with other cohorts. Therefore, we consider that our results might be the basis for comparison with future investigations.

In conclusion, multidisciplinary treatment using induction CAMP therapy and surgical resection for thymoma patients with pleural dissemination was effective. Because of the low recurrent rate of disease, patients with pleural disseminated nodules, who are young and well managed for their status of MG and had sufficient cardiopulmonary function, might be good candidates for EPP.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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