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Current chemotherapy options for thymic epithelial neoplasms

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Thymomas and thymic carcinoma are rare neoplasms. Surgical resection is the cornerstone of effective therapy. Stage I disease is effectively treated by complete surgical resection. The role of radiation therapy in completely resected stage II disease remains controversial. Adjuvant radiation therapy is useful for local control and may improve survival in patients with incompletely resected tumours. Cisplatin-based chemotherapy regimens play an important role in the treatment of advanced stage III/IV or recurrent disease thymomas, but have proven less effective for thymic carcinoma. Phase II trials of multimodality therapy incorporating neoadjuvant chemotherapy, surgery and postoperative radiation therapy show promise for unresectable disease. This review discusses recent clinical data and the potential role for agents targeting the epidermal growth factor receptor, angiogenesis and apoptotic pathways.

Keywords: chemotherapy, targeted therapy, thymic carcinoma, thymoma

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1. Introduction

Thymomas and thymic carcinomas are rare neoplasms of the thymic epithelium, characterised by histological heterogeneity. In the US, Surveillance, Epidemiology and End Results (SEER) data suggest an incidence of 0.15 per 100,000 person-years, with increased occurrence into the eigth decade of life and amongst Asians/Pacific Islanders. Incidence is higher in males [1]. The aetiology of thymomas is so far undetermined. Suggestions of a possible human T-cell leukemia virus-1 associated viral aetiology have not been substantiated [2]. Epstein–Barr virus is associated with lymphoepithelioma-like thymic carcinomas but causality remains to be established [3]. Clinically, one-third of patients are diagnosed incidentally with an anterior mediastinal mass on radiological imaging, one-third present with associated local symptoms including cough, dyspnea, superior vena caval syndrome or dysphagia, and one-third manifest with autoimmune syndromes, particularly myasthenia gravis (MG).

Classic thymomas have a bland histology and are distinguishable from thymic carcinoma, which has more typical pathological features of malignancy. Invasiveness determines the malignant propensity of thymoma. A number of histological classification systems have attempted to encompass the heterogeneous nature of thymomas. Most recently, the World Health Organization (WHO) Committee on the Classification of Thymic Tumours adopted a new classification system based on the cytological features of the thymic epithelial cells and proportion of lymphocytes [4]. This classification distinguishes medullary (type A), cortical (type B1, B2, B3), mixed (type AB) thymomas and thymic carcinoma (type C). Several studies have subsequently shown the new classification to be of use in predicting associated genetic abnormalities and prognosis in a clinically meaningful way [5-8]. Type A, AB and B1 tumours have better prognoses than type B2, B3 and C tumours, with the respective proportions of invasive tumour in patients with type A, AB, B1, B2 and B3 tumours being 11.1, 41.6, 47.3, 69.1 and 84.6% [7].

Table 1. Modified Masaoka staging of thymic epithelial neoplasms

Stage	
I	Macroscopically encapsulated and microscopically no capsular invasion
IIa	Microscopic transcapsular invasion
IIb	Macroscopic capsular invasion into surrounding fatty tissue, or grossly adherent but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighbouring organ
IVa	Pleural or pericardial dissemination
IVb	Lymphogenous or hematogenous metastasis

Recurrent karyotype abnormalities have been documented in thymomas, with distinct histological types exhibiting distinct genetic phenotypes [9]. Type A thymomas are homogeneous in showing chromosome 6q deletions including the *HLA* locus and p21. Type B2 and B3 thymomas have additional frequent chromosome 5q (adenomatous polyposis coli locus), 13q (retinoblastoma [*RB*] locus) and 17p (*p53* locus) deletions suggesting possible progression from B2 to B3 [6]. Amplifications detected at regions in chromosome 16 (cadherin-encoding gene [*CDH1*]) and chromosome 18 (*bcl-2*) and inactivation of RB may play a role in tumour progression in thymomas [10]. Using gene expression profiling Sakaki *et al.* have identified and shown a correlation of expression of a number of genes including adhesion molecule *cten*, *ets-1* oncogene and glycosylphosphatidyl inositol-anchored protein (*GPI-80*) with thymoma stage, suggesting a role in tumour invasiveness and metastasis [11-13].

The Masaoka staging system for thymoma is widely adopted and considers microscopic and macroscopic invasion, local and distant metastasis (**Table 1**). Stage correlated with prognosis, with 5-year survival rates of 92.6% in stage I, 85.7% in stage II, 69.6% in stage III and 50% in stage IV [14]. This staging system has been modified to define stage IIa tumours as transgressing the capsule, and IIb tumours as grossly adherent but not through the mediastinal pleura or pericardium [15]. Type A, AB and B1 tumours occur frequently in Masaoka stage I and II, whereas type B2, B3 and C are more commonly detected in stage III and IV [8]. Tumour stage and histological subtype are independent prognostic factors in thymoma.

2. Goal of therapy

The goal of therapy for thymomas is cure. This is more readily achieved in early stage disease, less so with stage III and infrequently in stage IV disease. Surgical resection is the mainstay of therapy and completeness of resection is an independent prognostic indicator of relapse and survival [16]. Radiation therapy is integral in the therapy of incompletely resected thymomas. Chemotherapy is advocated for unresectable stage III and IV thymomas.

If possible, complete surgical resection via median sternotomy is the treatment of choice in thymomas. Surgery is well tolerated, provided that intercurrent MG is well controlled and operative mortality is low. En bloc resection of major vessels with vascular reconstruction may be required to achieve complete resection in stage III disease, but can achieve excellent 5-year survival rates of 94% [17]. Recurrent thymoma is often limited to the thorax. The therapeutic goal with recurrent disease is to render the patient disease free. Surgical resection following recurrence has been shown to be a useful strategy, but results need to be interpreted in the context of the often indolent biological behaviour of the disease itself [18,19].

Complete surgical resection is achievable in almost all stage I and II patients. Disease-specific survival is almost 100% in completely resected stage I disease, and recurrence rate is < 1.6% [20-27]. The general consensus, with some dissenters, is that adjuvant radiation therapy is unnecessary for completely resected stage I disease. Less clear is the role for radiation therapy in stage II disease. Although some recommend radiation therapy for all stage II patients [21,22,24,28], others have proposed selective use depending on tumour size or histology [8,26]. Recurrence rates in patients without, or receiving adjuvant RT are in the range of 0 – 33 and 0 – 24%, respectively [24,27,29-31]. Two recent publications, albeit with relatively short follow up, have shown no significant difference in recurrence rates, nor overall, disease-free or disease-specific survival benefit to adjuvant radiation in stage II patients [27,30]. Pertinent to this debate are the efficacy of re-resection for patients with recurrent disease and the potential short and long-term sequelae of local radiation therapy.

The reported rate of resectability of stage III disease is highly variably, likely reflecting surgical acumen. Postoperative radiation therapy for resected stage III disease appears to decrease recurrence of disease in the radiation field [32,33]. Urgesi and colleagues report no in-field recurrences in 33 patients with completely resected stage III thymoma who received postoperative radiation [32]. Kondo and Monden, however, report no benefit to adjuvant therapy in reducing recurrence or outcome in completely resected stage III patients [31]. Thus, whether adjuvant radiation therapy in completely resected stage III patients translates into improved disease-free and overall survival (OS) rates remains to be tested in appropriately designed clinical trials. Radiation therapy is recommended for patients with incompletely resected advanced thymomas. Such patients receiving postoperative radiation therapy appear to have a similar disease-free and median survival rates to completely resected patients [34]. Although some studies suggest debulking surgery does not improve outcome in patients receiving radiation therapy for unresectable stage III/IV disease [21,35], other studies recommend debulking over biopsy alone when followed by radiation therapy [36]. For biopsied versus debulked tumours

followed by radiation therapy, 5-year survival rates are typically about 36 and 64%, respectively [31,36]. There is no consensus on whether patients with unresectable stage III disease and locally advanced stage IVa disease may benefit from induction radiation therapy, which can potentially reduce tumour bulk and facilitate resection. In selected patients with intrathoracic recurrence of thymoma treated with radiation, there was no significant difference in survival at 7 years in those receiving radiation therapy alone, as compared with combined resection and radiation therapy (65 versus 74%, respectively) [37]. The high rate of recurrence and poor survival rates in patients with incompletely resected tumours treated with radiation alone argue for more effective treatment strategies.

Chemotherapy is playing an increasing role in treatment of patients with stage III and IV disease and in those patients with disease recurrence not amenable to resection or radiation therapy. Numerous agents, either alone or in combination regimens, have been tested for activity in both thymomas and thymic carcinoma. This review details current chemotherapeutic options and potential future developments in the medical treatment of this intriguing malignancy.

3. Available compounds

A number of studies have demonstrated efficacy of chemotherapy, confirming the chemo-sensitive nature of thymoma. Traditional cytotoxic chemotherapy has been less successful in the treatment of thymic carcinoma. Many of the regimens used for thymoma have been used for thymic carcinoma. Unfortunately, data for the latter is even more sparse and confounded by the small numbers of patients treated and by the heterogeneity of thymic carcinoma [38]. Earlier studies of chemotherapy have provided the framework for more recent prospective trials in these thymic neoplasms [39-42].

3.1 Single chemotherapy agents

In a Phase II trial in 1993, the Eastern Cooperative Oncology Group (ECOG) reported minimal activity of single-agent cisplatin 50 mg/m^2 i.v. every 3 weeks in 21 patients with metastatic or recurrent thymoma. Response rate was 10%, with a median survival of 17 months and a 2-year survival rate of 39% [43]. The majority of patients had received prior radiation therapy and the dose of cisplatin may have been suboptimal, accounting for the disappointing response rate.

Single-agent ifosfamide (1.5 g/m^2 on days 1 – 5) with mesna every 3 weeks was evaluated in 17 patients with advanced (stage III – Vb) thymoma or thymic cancer [44]. Overall response rate for thymoma patients was 46.2% (complete response [CR]:5; partial response [PR]:1), with an estimated 5-year survival of 57%. Many patients treated in this trial received subsequent salvage chemotherapy, radiation therapy or surgery, thus confounding the outcome data.

3.2 Combination chemotherapy regimens

Cisplatin-based combination chemotherapy has been evaluated and activity confirmed in a number of series. A Phase II Intergroup trial found an overall response of 50% (CR:3, PR:12) in 30 patients with metastatic or recurrent thymoma or thymic cancer treated with cisplatin (50 mg/m^2), doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) (PAC) every 3 weeks [45]. The median duration of response was 11.8 months and median survival time 37.7 months. OS of 2 years was 64.5% and 5-year estimated OS was 32%.

In a Phase II Intergroup trial exploring the role of ifosfamide, 28 evaluable patients with advanced thymoma or thymic carcinoma received treatment with etoposide (75 mg/m^2 on days 1 – 4), ifosfamide (1.2 g/m^2 on days 1 – 4) and cisplatin (20 mg/m^2 on days 1 – 4) (VIP) every 3 weeks with granulocyte colony-stimulating factor support [46]. The dose of cisplatin was 80 mg/m^2 as opposed to 50 mg/m^2 in PAC. Although nine advanced thymoma patients (32%) achieved a PR, there was significant toxicity. The median duration of response was 11.9 months, the median OS was 31.6 months and the 2-year survival was 70%. Increased toxicity without apparent superior efficacy makes this regimen less appropriate for first-line therapy. A European Organisation for Research and Treatment of Cancer (EORTC) trial, reported by Giaccone, treated 16 chemonaive patients with recurrent or metastatic thymoma with cisplatin 60 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1, 2 and 3, every 3 weeks. Overall response was 56% (CR:5; PR:4). Median progression-free and OS times were 2.2 and 4.3 years, respectively [47].

The ADOC regimen (adriamycin 40 mg/m^2 and cisplatin 50 mg/m^2 on day 1, vincristine 0.6 mg/m^2 on day 2 and cyclophosphamide 700 mg/m^2 on day 4, every 3 weeks) was shown to result in overall response of 91.8% (CR:16; PR:18) in 37 patients with advanced stage III/IV disease studied retrospectively. Median duration of response and median survival were 12 and 15 months, respectively [48]. Similar response rates have been documented in prospective multimodality regimens incorporating ADOC as neoadjuvant chemotherapy.

Other newer chemotherapeutic agents have been used in thymic tumours. Anecdotal reports of responses with paclitaxel as a single-agent in a patient with recurrent thymoma [49], and partial response with paclitaxel and gallium nitrate or carboplatin and paclitaxel in recurrent thymoma have been published [50,51]. At present the ECOG is completing a Phase II study of carboplatin plus paclitaxel treatment in patients with advanced thymoma or thymic carcinoma.

3.3 Targeted therapy

As an alternative to conventional chemotherapeutic agents, targeted thymic-specific therapies have been investigated. First amongst these is prednisone, with reports in the early 1990s of single-agent activity of high-dose prednisone [52]. More recently, a role for somatostatin (SST) analogues has

been established in the treatment of chemoresistant thymomas. Thymic epithelial cells produce SST, and SST receptors are expressed by thymic malignancies. Octreotide, an octapeptide SST analogue, seems to inhibit thymic epithelial cell growth via insulin-like growth factor or epidermal growth factor blockade and, thus, target SST receptor expressing thymic tumours. Following complete remission in a patient with thymoma and red cell aplasia treated with octreotide and prednisone [53], Palmieri reported on 16 patients with advanced thymic tumours, unresponsive to conventional chemotherapeutic regimens receiving octreotide (1.5 mg/day s.c.) with prednisone (0.6 mg/kg/day p.o. for 3 months, 0.2 mg/kg/day p.o. during follow up). In eight cases, octreotide was replaced by the long-acting analogue lanreotide (30 mg every 14 days i.m.). The overall response rate was 37% (CR:1; PR:5). The median survival was 15 months, and median time to progression was 14 months. Treatment was well tolerated with acceptable toxicity and the long-acting analogue lanreotide improved patient compliance [54].

The ECOG completed a Phase II study testing the efficacy of octreotide in thymic tumours [55]. Patients were required to have positive radionuclide octreotide scans, and those failing to respond to octreotide alone also received prednisone. Of 32 thymoma patients treated with octreotide alone, response rate was 12.5% (PR:4). Overall response in patients receiving octreotide with or without prednisone was 31.6%, with a 2-year survival rate of 75.7%. There was no response to treatment in patients with thymic carcinoma.

3.4 Multimodality therapy

Patients with unresectable stage III/IV thymoma have a poor prognosis. Attempts to improve outcome have focused on combining different modalities of therapy, including chemoradiation and combination induction chemotherapy, followed by surgical resection, radiation therapy and consolidative chemotherapy.

The ECOG completed a trial in limited-stage unresectable thymoma patients, prospectively evaluating the efficacy of PAC followed by radiation therapy [56]. Patients with disease confined to one radiation portal received up to four cycles (repeated every 3 weeks) of PAC, followed by a total dosage of 54 Gy to the primary tumour and regional lymph nodes in patients with at least stable disease. Of 23 assessable patients, the overall response rate to PAC was 69.6% (CR:5; PR:11). The median time to failure was 93.2 months (range: 3 – 99.2 months), and the median survival was 93 months (range: 1 – 110 months). The 5-year survival rate is 52.5%. This study confirmed that combined-modality therapy is feasible. The prolonged progressive-free survival suggested a benefit of combined-modality therapy over radiation therapy alone, but a randomised trial is required to confirm this hypothesis.

Induction chemotherapy may facilitate surgical resection by cytoreduction of invasive tumours. As in many surgical instances, tumour resectability is a relative term that is dependant on surgical expertise. Without a clear definition of resectability, differentiating the efficacy of various induction chemotherapy approaches on the basis of attainment of complete resectability may be spurious. In an early prospective study of induction chemotherapy, seven patients with stage III thymoma were entered into a trial of induction chemotherapy followed by surgery and postoperative radiation therapy (46 – 60 Gy). Chemotherapy consisted of three cycles of cisplatin (75 mg/m^2 on day 1) epirubicin (100 mg/m^2 on day 1), and etoposide (120 mg/m^2 on days 1, 3 and 5), every 3 weeks. All patients showed a partial response to chemotherapy and 4 patients underwent complete resection. The projected 2-year survival was 80% [57].

Without a standardised multimodality approach, Venuta *et al.* achieved a 47% 10-year survival in patients with stage III thymic tumours [58,59]. To optimise therapy, they developed a multimodality approach including induction chemotherapy, surgical resection, postoperative radiation therapy and consolidative chemotherapy. A total of 45 patients with stage III thymoma and thymic carcinoma were treated prospectively [58,60]. All but three patients completed planned therapy, with one treatment-related death. A total of 30 patients with resectable stage III tumours underwent surgery. Fifteen patients deemed incompletely resectable received three cycles of induction chemotherapy (cisplatin 75 mg/m^2 day 1, epirubicin 100 mg/m^2 day 1, etoposide 120 mg/m^2 day 1, 3 and 5 every 21 days in eight patients; cisplatin 50 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 day 1 every 21 days in seven patients) prior to surgical resection. Response rate to induction chemotherapy was 66.6% (CR:2; PR:8) and two patients (13%) had incomplete resection after induction chemotherapy. All patients received consolidative chemotherapy and radiation therapy. Patients with complete resection received 40 Gy, with 50 – 60 Gy for incomplete resection. A dose-response effect from radiotherapy was not readily discernable. With prospective multimodality therapy, 10-year actuarial survival was improved at 78% and disease-free survival was 53%.

In a retrospective analysis, Rea *et al.* report on 70 patients with stage III and IVa thymomas treated surgically with or without induction chemotherapy. Of 38 patients proceeding directly to surgery, 58% had complete and 42% incomplete resection. In 32 patients with unresectable tumours receiving induction ADOC, overall response was 100% (CR:9; PR:22). Induction chemotherapy improved resection rates, allowing for complete resection in 75% of patients. Patients with viable tumour postsurgery received radiation therapy, whereas those demonstrating complete pathological response received additional chemotherapy [61,62]. Overall 10-year survival was 39% for those undergoing only surgery and 42% for patients receiving induction chemotherapy.

In a Phase II study, Kim *et al.* treated 22 chemotherapy-naive patients with unresectable stage III/IV invasive thymoma with a multimodality regimen consisting of three

cycles of induction chemotherapy (cyclophosphamide 500 mg/m^2 day 1, doxorubicin 20 mg/m^2 CI days 1 – 3, cisplatin 30 mg/m^2 days 1 – 3 and prednisone 100 mg days 1 – 5 every 3 weeks; CAP) followed by surgical resection [63,64]. Following tumour resection, patients received radiation therapy and three further cycles of consolidative therapy at 80% of induction doses for CAP. Response rate following induction therapy was 77% (CR:3; PR:14). With one exception, all patients underwent resection, which was complete in 16 (76%) and incomplete in 5 (24%). If resection was complete and tumour was > 80% necrotic, patients received 50 Gy of radiation. A dose of 60 Gy was administered if resection was incomplete or the tumour was < 80% necrotic. Of 22 patients, 19 completed planned therapy. With median follow up of 50.3 months, OS was 95% at 5 years (CI 0.87 – 1.0) and progressive-free survival was 77% at 5-years (CI 0.58 – 1.0). The regimen appeared to be tolerated, with no surgical mortality and myelosuppression as the major side effect of chemotherapy.

These trials demonstrate that induction chemotherapy facilitates surgical resection by achieving meaningful cytoreduction. Furthermore, combined modality therapy appears to improve outcome in patients with unresectable disease. Prospective randomised trials will be necessary to clearly define the best approach, including optimal modality sequencing, as well as clarification as to whether a dose-response effect from radiotherapy exists for selected patients.

4. Current best practice

A randomised Phase III trial comparing various active single agents or combination regimens for thymoma or thymic carcinoma has yet to be conducted. Many data are retrospective in nature and consequently, prospectively validated consensus recommendations on the optimal approach to chemotherapy in advanced stage thymomas are lacking.

For patients with unresectable stage III or IV thymomas, induction therapy with a cisplatin-based regimen should be considered. Although ADOC appears to produce superior response rates and may be most effective for induction chemotherapy, the choice between the various cisplatin-, adriamycin- and cyclophosphamide-containing regimens is likely to be made on the basis of personal preference and familiarity.

Surgical resection, where possible, followed by radiation therapy and consolidative chemotherapy should be offered to patients with localised disease shown to be chemo-responsive, particularly in those having histological subtypes with propensity for recurrence and metastasis. Patients unsuitable or unwilling to undergo chemoradiation, or refractory to chemotherapy who have positive radionuclide octreotide scans, can be offered an SST analogue and prednisone. Patients being considered for salvage chemotherapy should be encouraged to enter into clinical trials.

Optimal management of patients with thymic carcinoma has yet to be defined due to the paucity of the disease. At present, a multimodality approach similar to that for thymoma, involving aggressive surgical resection, platinum-based combination chemotherapy and radiotherapy, represents the preferred therapeutic approach.

5. Conclusions and future directions

The role of chemotherapy in thymomas has evolved from its use as salvage therapy following recurrence or metastatic disease, to it's current use in the neoadjuvant setting. This progression reiterates the need for determining the most effective therapy that provides for optimal outcome without compromising patient quality of life. Cisplatin-based regimens are a standard of care for thymic tumours, but randomised trials and further progress in identifying effective new active agents in this disease are needed.

The lack of cell lines derived from epithelial thymic tumours has hampered the *in-vitro* and xenograft testing of new drugs in thymic neoplasms. A number of novel agents targeting the apoptotic and receptor-mediated signalling pathways, particularly members of the human epidermal receptor (HER) family, are currently in clinical development or in clinical use. Thymomas of each WHO histological type have been analysed to elucidate pathways of pathogenesis, revealing proliferative and apoptotic pathway dysregulation. Consequently, several potential targets for therapeutic intervention have been identified.

Tyrosine kinase (TK) receptor expression has been studied in patients with thymic neoplasms. Overexpression of epidermal growth factor receptor (EGFR) was found in 69 – 74% of patients tested, particularly in WHO B2 and B3 subtypes [65-67]. Mutations in the TK domain of EGFR are strongly associated with sensitivity to TK inhibitors, such as erlotinib or gefitinib, in patients with non small cell lung cancer [68]. It is as yet unknown whether such mutations occur in thymic tumours.

Nonetheless, clinical benefit from therapy with EGFR TK inhibitors has been documented in lung cancer patients without EGFR mutations, suggesting a potential role for these agents in the treatment of EGFR-positive thymic tumours, even if these mutations are absent. C-Kit has also been studied in thymic tumours [69,70], revealing that thymic carcinoma typically express c-Kit (73 – 86%). The vast majority of thymic cancers tested so far show no c-Kit mutations, although an anecdotal case of thymic carcinoma with overexpressed and mutated c-KIT responding to imatinib suggests testing may be considered in such patients [71]. Pan *et al.* examined a panel of 63 thymomas and 17 thymic carcinomas but found no significant HER-2 expression in thymomas [72]. Although 50% of thymic carcinomas expressed > 2+ HER-2, no gene amplification could be documented by fluorescence in situ hybridisation.

The clinical utility of anti-HER-2 therapy such as trastuzumab is thus questionable.

There appears to be a correlation between tumour angiogenesis and the invasiveness in thymomas [73], with a correlation between microvessel density, vascular endothelial growth factor (VEGF) expression and Masaoka clinical stage. There is a suggestion of the presence of parenchymal microvessels in invasive thymomas, but not noninvasive thymomas. Increased circulating levels of VEGF and basic fibroblast growth factor are found in patients with thymic carcinoma, but not thymomas [74]. Anti-VEGF agents, such as bevacizumab, or VEGF receptor inhibitors, such as SU-11248, may be useful in patients with invasive thymoma.

In thymomas there is dysregulation of the apoptotic pathway [72]. Bcl-2 is an antiapoptotic protein that promotes tumour cell proliferation and is weakly expressed in type A and AB, absent in B1 and B2 thymomas, but strongly expressed in thymic carcinomas [72]. Furthermore, Fas protein is absent in thymic carcinomas but expressed by other thymoma types [75]. Survivin is another member of the inhibitors of apoptosis protein family involved in the control of cell division and inhibition of apoptosis. Survivin has been shown to be specifically upregulated in tumours and is expressed in 82% of thymic tumours tested, being absent only in B1 tumours [76]. The tumour suppressor p53 is expressed at low levels in thymomas and overexpressed in thymic carcinomas. [72,76]. Survivin functions as an upstream regulator of p53 mitochondrial-dependent apoptosis. Targeting of the survivin pathway results in anticancer activity via a dual mechanism of induction of tumour cell apoptosis and suppression of angiogenesis [77]. Bcl-2 and survivin may thus be targets for antitumour intervention in thymic neoplasms.

6. Expert opinion

The contribution of chemotherapy and radiation therapy to improving outcome in advanced thymoma patients still remains to be clearly defined, as does the best means of incorporating these modalities into treatment protocols. Countless publications lament the lack of randomised trials in the treatment of thymic epithelial neoplasms. Although thymic tumours are rare, the number of patients reported in individual studies suggests that a concerted national and international effort may well accomplish this goal. An acceptable and clinically relevant histological and staging system is now in place, which should facilitate patient entry to and comparison of clinical trials. Patients who fail initial therapy should be encouraged to enter clinical trials. As with the Sarcoma Research Consortium initiative, a new model of clinical research in thymoma encompassing all disciplines, modalities and current technologies needs to be adopted by clinicians, researchers and patients. The American College of Surgeons Oncology Group Thoracic Committee is developing prospective, multi-institutional trials for both early and locally advanced thymic neoplasms.

Advances in molecular techniques can further elucidate the nature of thymoma types and help define molecular targets of therapy. As previously discussed, several such targets and potential therapies have already become apparent. The need to explore these in a prospective manner is obvious.

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