Thymic Carcinoma

Subjects: Allergy

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Thymic epithelial tumors consist of thymoma and thymic carcinoma (TC), which are rare neoplasms. Notably, TC is a dismal entity that easily depicts recurrence after surgical resection. In patients with metastatic or advanced TC, systemic chemotherapy is widely chosen to decrease tumor growth and metastasis.

Keywords: thymic carcinoma ; salvage chemotherapy

1. Introduction

Thymic epithelial tumors consist of thymoma and thymic carcinoma (TC), which are rare neoplasms. Notably, TC is a dismal entity that easily depicts recurrence after surgical resection. In patients with metastatic or advanced TC, systemic chemotherapy is widely chosen to decrease tumor growth and metastasis. but the tumor is frequently resistant to chemotherapy. To date, a combination of platinum-based regimens is administered to patients with TC as a first-line setting; however, it remains debatable which regimens are appropriate for such patients in terms of efficacy and survival. Despite no formal evidence of survival benefits with salvage chemotherapy, its use is widely supported by clinical practice and high disease control rate. However, many patients are treated with salvage chemotherapy.

2. First-Line Chemotherapy in TC

As appropriate chemotherapeutic regimens in the first-line setting, platinum-based chemotherapy has shown some active efficacy and tolerability in patients with thymic epithelial tumors, including thymoma and TC. A recent review described that combinations of cisplatin-anthracycline or cisplatin-etoposide are recommended as first-line chemotherapy in such patients [1]. **Table 1** shows a summary of platinum-based chemotherapy as first-line treatment in patients with advanced TC. Previous studies have identified that cisplatin-adriamycin-cyclophosphamide (CAP), cisplatin-doxorubicin-cyclophoshamide-vincristine (ADOC), cisplatin-etoposide (VP16), cisplatin-docetaxel, and carboplatin-paclitaxel are the most common regimens administered in patients with TC [1][2][3][4][5][6][7][8][9][10][11][12][13]. The overall response rate (ORR) of platinum-based chemotherapy was yielded approximately 30–40% (from 21% to 70%), regardless of the small sample size. Although high-intensity regimens, such as CAP or ADOC, increase the response rate, severe adverse events were also observed, although CAP is a standard regimen at least in Europe for thymoma [2][3][4][5][6][7][8]. Meanwhile, cisplatin plus etoposide or carboplatin plus paclitaxel are commonly administered to patients with advanced non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), known as active and tolerable regimens. Unfortunately, multidrug chemotherapy such as ADOC or CAP has been clarified as a toxic regimen, regardless of its high efficacy. Nowadays, the useful frequency of these heavy regimens gradually decreases due to the lack of significant improvement in the outcome compared to cisplatin plus etoposide or carboplatin plus paclitaxel. Considering the results of previous studies (**Table 1**), the number of patients with TC registered in individual studies showed small sample sizes; therefore, it remains unclear which regimen is better as a standard treatment. However, the histological type of patients with TC predominantly consists of squamous cell carcinoma, similar to that of NSCLC. Recently, Ko et al. retrospectively analyzed the prognostic factors and efficacy of first-line chemotherapy in 286 patients with advanced TC in a multi-institutional study [14]. In their study, the administration frequency of platinum-based doubles, monotherapy, and other multidrug chemotherapy such as ADOC was 62.2%, 3.5%, and 34.3%, respectively, and there was no significant difference in overall survival (OS) between different first-line therapeutic regimens (between carboplatin plus paclitaxel and ADOC, median OS: 27.8 vs. 29.9 months) [14]. Of the 286 patients, carboplatin plus paclitaxel was administered to 70 patients with an ORR of 49%, cisplatin plus etoposide in 35 patients (ORR, 48.6%), cisplatin plus irinotecan in 16 patients (ORR, 66.7%), carboplatin plus etoposide in 15 patients (ORR, 30.8%), and cisplatin plus docetaxel in nine patients (ORR, 22.2%). As with other multidrug chemotherapy, the 79 patients who received ADOC achieved ORR of 41% and CAP were administered to eight patients with an ORR of 37.5%. They concluded that the efficacy of individual first-line regimens against advanced TC was not significantly different, and the use of carboplatin plus paclitaxel might be adequate as first-line chemotherapy [14]. In terms of efficacy,

tolerability, and histological similarity, carboplatin plus paclitaxel seems appropriate as first-line chemotherapy for patients with TC.

Table 1. Reports of platinum-based regimens as first line setting in thymic carcinoma.

First Author (Year)	Ref.	Regimens	Thymoma + TC		TC	
			N	ORR (%)	*N*	ORR (%)
Platinum-anthracycline based chemotherapy						
Kim (2004)	[4]	CAP	22	77%	12	NA
Li (2007)	[2]	CAP	28	71%	18	61%
Cardillo (2010)	[3]	CAP	21	58%	10	50%
Agatsuma (2011)	[5]	ADOC	NA	NA	34	50%
Rea (2011)	[6]	ADOC	38	68%	6	50%
Yoh (2003)	[15]	CODE	NA	NA	12	42%
Oshita (1995)	[7]	CAP-VP16	14	43%	7	42%
Thomas (2014)	[8]	CAP-belionstat	26	40%	14	21%
Platinum-etoposide based chemotherapy						
Loehrer (2001)	[9]	CDDP+VP16-IFO	28	32%	8	NA
Grassin (2010)	[10]	CDDP+VP16-IFO	16	25%	4	25%
Platinum-taxane based chemotherapy						
Park (2013)	[11]	CDDP-DTX	27	63%	18	66%
Kim (2015)	[12]	CDDP-PTX	42	63%	28	70%
Lemma (2011)	[1]	CBDCA-PTX	44	32%	23	21.7%
Igawa (2010)	[13]	CBDCA-PTX	NA	NA	11	36%
Furugen (2011)	[16]	CBDCA-PTX	NA	NA	16	37.5%
Hirai (2015)	[17]	CBDCA-PTX	NA	NA	39	35.9%
Platinum-doublet other chemotherapy						
Okuma (2011)	[18]	CDDP-irinotecan	NA	NA	9	55.6%
Luo (2016)	[19]	CDDP-gemcitabine	NA	NA	13	61.5%

Abbreviations: Ref., reference; TC, thymic carcinoma; ORR, overall response rate; *N*, number of patients; CAP, cisplatin-adriamycin-cyclophosphamide; ADOC, cisplatin-doxorubicin-cyclophosphamide-vincristine; CODE, cisplatin-vincristine-doxorubicin-etoposide; VP16, etoposide; IFO, ifosfamide; DTX, docetaxel; CDDP, cisplatin; PTX, paclitaxel; CBDCA, carboplatin; NA, not applicable.

3. Cytotoxic Agents as Salvage Chemotherapy

Due to their rarity, there are limited reports on salvage chemotherapy for patients with previously treated advanced TC [20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49]. Owing to the limited number of studies and small sample sizes, it is difficult to determine the most effective therapeutic regimen for such patients. Of several chemotherapeutic regimens, S-1, amrubicin, docetaxel, paclitaxel, gemcitabine, etoposide, sunitinib, everolimus, and lenvatinib have been reported as active drugs in previously treated patients with TC. Recently, Tateishi et al. retrospectively analyzed the clinical outcomes of 191 patients with previously treated advanced TC [25]. As second-line chemotherapy in their study, platinum-based doublets, multidrug chemotherapy (e.g., ADOC), and monotherapy were observed in 57.6%, 13.6%, and 28.8%, respectively. The median OS at the initiation of second-line chemotherapy was 22.4 months, and the average ORR was 20.0% (ORR and median OS were 21.6% and 22.4 months, respectively, in platinum-based doublet chemotherapy, 13.6% and 25.7 months, respectively, in other multidrug chemotherapy and 19.6% and 21.4 months, respectively, in monotherapy). The results of their study indicated that there was no significant

difference in ORR and OS between each regimen. Therefore, compared to combination chemotherapy, monotherapy could be easily and safely administered to patients with advanced TC as a second-line treatment.

4. Molecular Target Agents as Salvage Chemotherapy

Molecular targeting drugs, such as vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors, have been explored in patients with recurrent TC [50][51][52][53][54]. As these targeting agents can efficiently kill tumor cells by disrupting their signaling pathways, they may contribute to longer survival without severe toxicities.

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