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ORIGINAL ARTICLE

Therapy of stage IV B anaplastic thyroid carcinoma: single institution experience

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Summary

Purpose: *To evaluate the efficacy of radiotherapy and chemotherapy in stage IV B anaplastic thyroid carcinoma (ATC).*

Patients and methods: *From 1997 to 2007, 16 inoperable patients (12 females, 4 males, median age 60 years, range 27-71) with pathologically confirmed ATC without distant metastases (UICC stage IV B) were treated with radiotherapy and chemotherapy at our Institution. Five patients had Eastern Cooperative Oncology Group (ECOG) performance status 1, and 11 ECOG 2. All patients received the planned radiotherapy tumor dose of 60 Gy. Radiotherapy was followed by chemotherapy with doxorubicin 60 mg/m^2 and cisplatin 40 mg/m^2 every 3 weeks. The primary study endpoint was response rate (RR) and secondary endpoints were toxicity and overall survival (OS).*

Results: *Only one patient achieved complete response (CR: 6.25%, 95% CI: 0-35) and 3 patients (18.75%, 95% CI: 4-46) partial response (PR), for an overall response rate (ORR) of 25% (95% CI: 7-55). No toxic deaths occurred and no grade 4 adverse events were registered after radiotherapy. Grade 4 toxicity was seen in 3 patients (18.75%, 95% CI: 4-46) after chemotherapy. Mean patient OS was 12.33 months (95% CI: 9.09-15.56) and median OS 11.0 months (95% CI: 8.56-13.44).*

Conclusion: *Radiotherapy and chemotherapy of stage IV B anaplastic thyroid carcinoma are well tolerated. Although the clinical benefit was 50%, survival rates remain low with OS of no more than 2 years.*

Key words: anaplastic thyroid carcinoma, chemotherapy, radiotherapy, response, survival, toxicity

Introduction

ATC accounts for 5-15% of primary malignant thyroid neoplasms [1]. Although exceedingly rare, it is one of the most aggressive human malignancies that resists most therapeutic efforts and is almost always fatal [2,3]. ATC represents over half of thyroid cancer-related deaths [4] and typically comes as a terminal dedifferentiation of unrecognized long-standing differentiated thyroid carcinoma [5,6], most commonly of the papillary type [7,8]. So far, p53 and β-catenin mutations are the only genetic alterations that have been implicated in its pathogenesis [8]. Also, frequent allelic losses at multiple loci may implicate chromosomal instability as an important factor in the development of ATC [9]. Most patients are elderly, with a rapidly growing fixed mass. Enlarged lymph nodes and invasion of adjacent organs (trachea, esophagus, vessels and muscles) are frequently observed [10]. Almost half of the patients have distant metastases, with as many as 75% developing such metastases during their illness [11]. Distant metastases are chiefly in the lungs but also in bones, liver and brain [12]. Compressive symptoms including hoarseness, dyspnea, cough and dysphagia are frequent. Complete surgical resection is not possible in the majority of the patients. Diagnosis of ATC should be established by surgical biopsy. Only combined multimodality therapy can have a favorable impact on the local control rate, thus avoiding death from suffocation. Therefore ATC challenges clinicians and researchers to develop effective local and systemic therapies.

The aim of this study was to evaluate the efficacy of radiotherapy followed by chemotherapy in stage IV

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B anaplastic thyroid carcinoma patients in terms of RR and OS.

Patients and methods

From 1997 to 2007, 16 patients with inoperable ATC without distant metastases (UICC stage IV B) were treated with radiotherapy and chemotherapy at our institution. All of them had pathologically confirmed ATC. There were 12 female and 4 male patients with median age 60 years (range 27-71). Five patients had ECOG performance status 1, and 11 ECOG 2.

All patients were planned to receive photon radiotherapy to the primary tumor and bilateral neck with 2.0 Gy daily, 5 days per week up to 45 Gy with a boost of 15 Gy to residual disease with electron beams. They were also planned to receive photon radiotherapy up to 45 Gy to the upper mediastinum. Radiotherapy was followed by chemotherapy with doxorubicin 60 mg/m^2 and cisplatin 40 mg/m^2 every 3 weeks. Response to therapy was assessed using modified RECIST criteria with response durability acceptable at 2 or more weeks, due to the exceedingly rapid growth rate of this tumor [13]. Clinical benefit (CR+PR+stable disease/SD) was also evaluated. Toxicity was assessed using NCI common toxicity criteria (CTC), version 2.0.

The primary endpoint was RR. Secondary endpoints were toxicity and OS.

Statistical considerations

Survival was calculated from treatment initiation until death from any cause. Mean and median overall survival were calculated. The Kaplan-Meier method was used to estimate time to event curves. Patients who were alive on the day of last update were censored.

Results

Compliance with treatment and toxicity

All patients received the planned radiotherapy tumor dose of 60 Gy. Main radiation toxicities were dermatitis, laryngeal mucositis, pharyngeal dysphagia and pain (Table 1).

Patients received 3-7 chemotherapy cycles and the total number of chemotherapy cycles given was 79. The number of cycles per patient is shown in Table 2.

The main chemotherapy toxicities were gastrointestinal (nausea, vomiting), blood/bone marrow (leukocytes, hemoglobin, platelets), cardiovascular (left ventricular function), renal (creatinine) and alopecia. Grade 4 toxicity was noted in 3 patients (18.75%; 95% CI: 4-46) and was treated with ondansetron (vomiting), G-CSF (leukopenia) and blood transfusion (anemia). All toxicities are shown in Table 3. No toxic deaths occurred.

Response and survival

After radiotherapy and chemotherapy one patient achieved CR (6.25%, 95% CI: 0-35) lasting for 3 months. Three patients achieved PR (18.75%, 95% CI: 4-46) lasting for 10, 11 and 13 months. Four patients showed SD (25%, (95% CI: 7-75) and 8 patients had progressive disease (PD) (50%, 95% CI: 27-73; Table 4). Clinical benefit was achieved in 8 patients (50%, 95% CI: 27-73).

Kaplan-Meier curve of OS is shown in Figure 1. Mean patient OS was 12.3 months (95% CI: 9.09-15.56) and median OS 11.0 months (95% CI: 8-56-13.44). Two patients were censored.

Table 1. Number of patients with radiotherapy-related toxicity

Toxicity	*Toxicity grades*				
	0	*1*	*2*	*3*	*4*
Dermatitis	4	6	2	4	–
Laryngeal mucositis	1	8	4	3	–
Pharyngeal dysphagia	1	8	7	–	–
Pain	–	9	7	2	–

Table 2. Number of cycles per patient.

Number of cycles	*Patients*	*%*
3	5	31.25
4	3	18.75
6	4	25.00
7	4	25.00

Table 3. Number of patients with chemotherapy-related toxicity

Toxicity	*Toxicity grades*				
	0	*1*	*2*	*3*	*4*
Nausea	–	3	7	6	–
Vomiting	1	2	5	7	1
Leukocytes	–	6	7	2	1
Hemoglobin	–	7	6	2	1
Platelets	11	3	2	–	–
Left ventricular ejection fraction	6	5	5	–	–
Creatinine	12	3	1	–	–
Alopecia	2	4	10	–	–

Table 4. Response after radiotherapy and chemotherapy

Response	*Patients, n*	*%*	*95% CI*
CR	1	6.25	0-35
PR	3	18.75	4-46
SD	4	25.00	7-55
PD	8	50.00	27-73
Overall response	4	25.00	7-55

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, 95% CI: 95% confidence interval

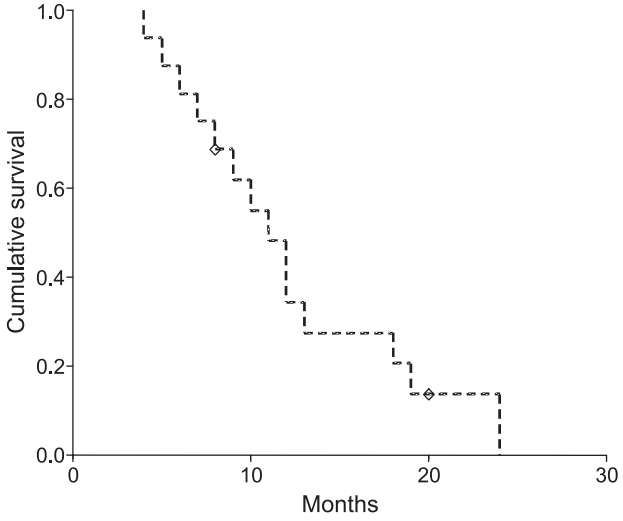

Figure 1. Overall survival with radiotherapy and chemotherapy. Mean 12.33 months (95% CI: 9.09-15.56). Median 11.00 months (95% CI: 8.56-13.44).

Discussion

Our results show that only one patient achieved CR and 3 patients PR, for an ORR of 25%. Yet, the clinical benefit (CR+PR+SD) of 50% shows that half of the patients were benefited from this therapy. In other studies this kind of therapy for ATC is also recommended for stage IV B [14].

No toxic deaths occurred. No grade 4 adverse events were seen after radiotherapy, whereas grade 4 toxicity was noted in 3 (18.75%) patients after chemotherapy. In many clinical trials where concomitant chemoradiotherapy was used, toxicity was much greater than in our study [15,16]. Furthermore, the doses of radiotherapy as well as the doses of chemotherapy were significantly lower compared with our trial [17].

The mean OS of our patients was 12.33 months. Lower mean OS was reported by many authors, even with surgery [18-21]. The median OS of our patients was 11.0 months. Lower median OS was also reported even when multimodal treatment, including palliative resection, was used [22,23] but direct comparison cannot be done because those studies included patients with metastases too.

Surgical intervention is still a matter of debate. While some authors propose surgery as the initial treatment of ATC, others speak in favor of its use after radiotherapy and chemotherapy [24,25].

Postoperative radiotherapy can produce slightly longer, but not statistically significant, median survival [26]. But if the radiation dose is greater than 45 Gy, the improved survival is statistically significant compared with a lower dose [27].

All aspects considered, prognosis of ATC remains dismal. The current treatment of ATC has not improved the prognosis or outcome, regardless of the modality used. Future studies with novel molecular targeted therapies [28,29], gene therapy approaches, oncolytic viruses and new cytotoxic drugs [30], remain the only hope to change the outcome of this aggressive malignancy.

Conclusion

Radiotherapy and chemotherapy of stage IV B anaplastic thyroid carcinoma are well tolerated. Although the clinical benefit was 50%, survival was low, with OS of no more than 2 years. New treatment modalities are desperately needed and promising molecular-based therapies will hopefully improve the therapeutic outcomes.

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