Anaplastic carcinoma of the thyroid: treatment and outcome over a 13 year-period at one institution.

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INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is a highly aggressive, although rare, malignancy of the thyroid gland, accounting for less than 4% of all thyroid cancers\textsuperscript{1,2}. Despite its infrequency, ATC comprised more than half of all thyroid cancer deaths in The United States in 2006\textsuperscript{3}. The disease is one of the elderly, only occasionally affecting persons below 60 years of age\textsuperscript{4,5}. ATC is generally thought to arise from a well-differentiated thyroid carcinoma\textsuperscript{6}; but whereas the worldwide incidence for differentiated thyroid carcinomas has increased over the past decades, the opposite appears to be true for ATC\textsuperscript{7}. This may attribute to iodine prophylaxis\textsuperscript{8}, but also to earlier diagnosis and improved treatment regimens for differentiated thyroid cancers\textsuperscript{7}. Long-term survival (>5 years) for ATC patients is below 7\%\textsuperscript{9}.

ATC presents as a rapidly expanding tumor mass in the neck, causing breathing difficulties and dysphagia. Untreated, the tumor permeates surrounding tissues, compresses vital structures, and ultimately strictures the trachea. The aim of treatment is not primarily to prolong survival, but to achieve local disease control, thereby preventing death by suffocation.

Treatment

At our institution, several multimodal treatment regimens have been used since 1971\textsuperscript{5}, when the first uniform treatment protocol was established. Up to 1975, combined radiotherapy (30 – 40 Gy over three to four weeks) and several chemotherapeutic agents (bleomycin or methotrexate, combined with 5-flourouracil, cyclophosphamide, vinblastine, or folic acid, respectively) were used; surgery was only performed on a few. From 1975 – 1983, surgery was considered for all patients when feasible, combined with hyperfractionated (1.0 Gy, two fractions/day) radiotherapy up to 46 Gy, divided into 30 Gy pre-operatively and 16 Gy post-operatively, and chemotherapy (bleomycin, cyclophosphamide and 5-fluorouracil). Doxorubicin was introduced as the chemotherapeutic agent in 1984, administered intravenously weekly at a dose of 20 mg, replacing other cytostatic drugs. To decrease the total time of treatment, radiotherapy was accelerated in 1989, by increasing each fractionated dose (to 1.3 Gy) pre- and post-operatively.

In accordance with the current treatment protocol, employed since 1994, all radiotherapy is administered preoperatively, further accelerating the dose to 1.6 Gy per fraction\textsuperscript{5,10}. Doxorubicin is administered in the same manner as for earlier protocols (Figure 1). Additionally, some patients continue Doxurubicin treatment post-operatively.

Doxorubicin was adopted in 1984 as the solitary chemotherapeutic agent, when shown to significantly diminish side effects compared with other chemotherapy\textsuperscript{11}. Doxorubicin also works synergistically with radiotherapy, radiosensitizing tumor cells by mechanism still unknown\textsuperscript{12}. 
Between 1984 and 1999, 40 ATC completed the treatment protocol, including surgery, at Karolinska and Lund University Hospitals. Local recurrence was observed in seven patients only, none of whom were treated according to the current regimen. Seventeen patients underwent the present protocol; none of these suffered from local recurrence, suggesting that local disease control is possible to accomplish.

Regardless of development in treatment regimens and improved locoregional control, median survival has not changed over the past decades. This has provoked a need for further therapy, for which reason bevacizumab (Avastin®), in 2010, has been introduced as a neoadjuvant supplement to the treatment protocol. The efficacy of Avastin as part of the ATC treatment regime is currently being evaluated.

Pathogenesis

Today, it is generally recognized that ATC most likely is an anaplastic transformation, or a dedifferentiation, of a pre-existing well-differentiated thyroid carcinoma (WDTC). ATC typically presents in an elderly individual, sometimes with a history of a well-differentiated thyroid cancer, contributing to this theory. Often, the patients have had longstanding multinodular goiters preceding the development of ATC. Underlying molecular mechanisms of tumorigenesis are not fully understood although several mutations involved in the process have been described.

Cell cycle abnormalities, hypoxia and DNA damage activate p53, a tumor suppressor protein known to inhibit excessive angiogenesis and cell growth, as well as induce DNA repair and, if needed, apoptosis. Mutations in TP53, the gene of p53, are common in several human cancers and present in more than half of all ATC tumors. Reintroduction of wild type TP53 results in redifferentiation of ATC tissue, providing further evidence of its role in ATC tumorigenesis.

Viglietto et al showed that vascular endothelial growth factor (VEGF) is redundantly expressed in ATC cell lines compared with normal thyroid tissue. Cell proliferation has also been shown to increase proportionally to VEGF expression. Therefore, adding VEGF inhibitors, for example bevacizumab, to treatment seems as a natural...
approach to try to minimize angiogenesis. In fact, angiogenesis was inhibited in an in vivo model of ATC by use of monoclonal antibodies against VEGF, adding credence to this theory\textsuperscript{21}.

The transcription factor NF-κB is greatly activated in all thyroid carcinomas, and especially in ATC\textsuperscript{24}, controlling expression of genes associated with cellular proliferation. In one study\textsuperscript{25}, NF-κB was inhibited in an ATC-derived cell line, resulting in downregulation of several micro-RNAs (miRNAs). Oncogenic effects were decreased, whereas the susceptibility to apoptosis-inducing drugs was increased, suggesting some oncogenic effects of NF-κB might be mediated by miRNAs.

It should be pointed out, however, that although ATC arising as a transformation from a WDTC is the most common theory of carcinogenesis, it is not the only one. For instance, one study showed that only 13.5 % in a group of 126 ATC cases contained foci of WDTC, indicating that the tumor cells developed \textit{de novo} rather than through dedifferentiation from a WDTC\textsuperscript{26}. Furthermore, although ATC and a WDTC might co-exist, this is not necessarily evidence of a dedifferentiation process. Foci of occult papillary carcinomas are in fact common among the general population, with a prevalence rate ranging from 5-36%, depending on geographical area and method used\textsuperscript{27-29}.

**MATERIALS AND METHOD**

Clinical data from 44 patients, diagnosed with ATC at Karolinska University Hospital in Stockholm during the time period February 1997 - March 2010, were collected and analyzed. Patients were identified from endocrine and histopathological databases, respectively. Thirty-nine patients were diagnosed with ATC through fine needle aspiration biopsy (FNAB), three patients through examination of the surgical specimen and an additional two were diagnosed at autopsy and were therefore excluded from the study. Diagnosis by FNAB was in most cases confirmed at histopathological examination of the surgical sample; however this was not always possible due to effects on the tumor tissue from preoperative chemo- and radiotherapy.

Data was retrieved retrospectively from clinical, surgical and histopathological medical records. Sex, age at diagnosis, treatment modality, type of operation, metastases at presentation, extrathyroidal invasion, thyroid disease in the medical history, thyroid disease in the family, macroscopic surgical radicality, histopathological radicality, post-operative metastases, and local recurrence were recorded. Patients who underwent the full program including pre-operative chemotherapy, radiotherapy and surgery with or without post-operative chemotherapy were classified as fulfillers of the treatment protocol. At follow-up, the following parameters were recorded: alive with ATC, alive with no signs of ATC, deceased from local tumor growth, deceased from metastases, deceased from other disease with ATC, deceased from other disease with no signs of ATC.

Statistical analysis of survival was made using SPSS Software (SPSS 15.0, IBM). Significance was calculated according to the log-rank test, and p-values <0.05 were considered as significant.
RESULTS

Among patients diagnosed through FNAB and/or histopathological examination of the surgical specimen, 35 underwent the complete treatment protocol for ATC, including pre-operative chemotherapy, pre-operative radiotherapy and surgery. Five could not complete treatment or were not treated at all; and two received pre-operative treatment and surgery for a differentiated thyroid carcinoma (Table 1). Age at diagnosis ranged from 49 to 94, with a median of 72.5. 27 patients (64%) were female and 15 patients (36%) were male.

Foci of well-differentiated thyroid carcinomas were found in the surgical specimen of 16 patients (38.1%). Ten were papillary thyroid carcinomas and six were either follicular or Hürthle cell carcinomas.

Thirty-two patients made an attempt to estimate the date of presentation of symptoms. Mean time from debut of symptoms to date of diagnosis was 56 days (median 35).

Table 1. Treatment specifics among patients with ATC, 1997 - 2010 (N=42).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean and range</td>
<td>73 (49 - 94)</td>
</tr>
<tr>
<td>Radiotherapy¹, Doxorubicin², surgery, and additional</td>
<td>19</td>
</tr>
<tr>
<td>Postoperative Doxorubicin</td>
<td>13</td>
</tr>
<tr>
<td>Postoperative Doxorubicin, Avastin</td>
<td>2</td>
</tr>
<tr>
<td>Other postoperative treatment</td>
<td>1</td>
</tr>
<tr>
<td>Discontinued radio- and chemotherapy, or no treatment at all</td>
<td>5</td>
</tr>
<tr>
<td>Treatment (including surgery) for differentiated thyroid cancer</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
</tr>
</tbody>
</table>

¹46 Gy, hyperfractionated ²20 mg intravenously, administered weekly

Table 2. Mean, range and median survival time (months) among different treatment groups.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
<th>Mean survival (range)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment protocol completed¹</td>
<td>35</td>
<td>12 (1 - 148)</td>
<td>5</td>
</tr>
<tr>
<td>Discontinued radio- and chemotherapy, or no treatment at all</td>
<td>5</td>
<td>0 (0 - 1)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment (including surgery) for differentiated thyroid cancer</td>
<td>2</td>
<td>4 (1 - 8)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>10 (0 - 148)</td>
<td>5</td>
</tr>
</tbody>
</table>

¹Completed treatment regimen was defined as pre-operative chemo- and radiotherapy, and surgery, with or without post-operative treatment.

Table 3. Follow-up data.

<table>
<thead>
<tr>
<th>Completed treatment protocol, N = 35</th>
<th>No treatment, discontinued treatment or treatment according to other protocol, N = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive with ATC</td>
<td>1</td>
</tr>
<tr>
<td>Alive with no signs of ATC</td>
<td>3</td>
</tr>
</tbody>
</table>
Table 4. Treatment data of survivors.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>78</td>
<td>71</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>Surgery</td>
<td>Lobectomy, contralateral resection</td>
<td>Total thyroidectomy</td>
<td>Lobectomy, lymph node resection</td>
<td>Total thyroidectomy</td>
</tr>
<tr>
<td>Radiality, microscopically</td>
<td>Uncertain</td>
<td>Yes</td>
<td>Uncertain</td>
<td>Yes</td>
</tr>
<tr>
<td>Neoadjuvant treatment</td>
<td>None</td>
<td>Doxorubicin</td>
<td>None</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>148</td>
<td>49</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Status</td>
<td>Alive with no signs of ATC</td>
<td>Alive with distant metastases</td>
<td>Alive with no signs of ATC</td>
<td>Alive with no signs of ATC</td>
</tr>
</tbody>
</table>

Figure 2. Survival function of the entire cohort. Ovals represent patients still alive. N = 42
Figure 3. Survival function showing patients completing (green line) and not completing (blue line) the treatment protocol. Ovals represent patients still alive.

Survival

Median time from diagnosis to last follow-up or death was 4.7 months (0.1 – 148.2) for the entire cohort, 4.3 months for the deceased (0.1 – 22.3), and 32.2 months (8.6 – 148.2) for patients still alive. Figure 2 shows a survival function of the entire cohort.

Completing the treatment protocol brought about a median follow-up or survival time of 5.3 months (1.4 – 148.2), compared with discontinuation of or no treatment, which was 0.1 months (0.1 – 0.8). This difference is significant (p<0.001) and summarized in Table 2 and Figure 3. Median survival for females was 3.3 months and 4.8 months for males. There was no difference in follow-up time or time from diagnosis to death between the younger and the older half of the group.

As demonstrated in Table 3, 25 patients died with distant metastases present but without any evidence of local tumor growth – all but three completing the treatment protocol (two initially treated for papillary thyroid carcinomas). Further, five patients succumbed to local tumor growth, only one of which completed the treatment protocol, including surgery. In this case, the tumor – extending caudally to the clavicle and sternum; adherent to esophagus, trachea and the carotid artery – was incompletely resected at the primary operation.

Seven patients died from unknown causes, all completing the treatment protocol. At last follow up, four had no signs of disease; two had progression of distant metastases already present at diagnosis; and one had a local relapse. Follow-up ranged from 22 –
226 days (median 40 days) prior to death. One patient deceased secondary to unrelated conditions without any signs of ATC 66 days after diagnosis.

Among patients alive, three had no evidence of disease at last follow-up (9, 15 and 148 months from diagnosis, respectively), and one had developed distant metastases at last follow-up (49 months). All survivors completed the treatment protocol. Two were radically operated microscopically and radicality was uncertain in the others, as summarized together with other treatment characteristics in Table 4.

Patients with a co-existent WDTC in the surgical specimen showed a median survival time of 4.7 months (0.1 – 9), thus not differing from the rest.

Several other factors were analyzed, as described in the method and materials section. None of these showed any impact on survival (data not shown).

DISCUSSION

ATC, the most aggressive carcinoma of the thyroid gland, presents as a rapidly expanding tumor mass causing dysphagia and dyspnoea. It is a rare malignancy, constituting only four percent of all thyroid cancers\(^1,2\). At our institution, an average of three patients diagnosed with ATC are admitted every year. In this study, time from presentation of symptoms to date of diagnosis was short. This corresponds well with earlier publications but must, however, be regarded with wariness because of the obvious difficulties in estimating such an interval.

Since 1971, several multimodal treatment regimens have been used at the Karolinska University Hospital\(^5\). Initially, radiotherapy was given as one 1.0 Gy fraction per day, up to 30–40 Gy, divided into pre- and postoperative portions. Because of the aggressive growth of ATC and to reduce tumor size as much as possible pre-operatively, the logical step was to decrease the total time of treatment. Thus, radiotherapy has since 1994 been given as hyperfractionated doses (1.6 Gy twice daily) and exclusively administered preoperatively. In 1983, when shown to significantly reduce side effects\(^11\), doxorubicin was adopted as the cytostatic agent of choice and has been used as part of the treatment protocol since then.

In spite of the development toward an accelerated and more aggressive treatment, survival time among ATC patients has remained unchanged\(^14\). Apparently, current therapy is not sufficient to prolong life expectancy.

The importance, however, of a multimodal treatment regimen as palliative therapy must be emphasized. Local relapse ultimately results in compression of the trachea and the patient will die from suffocation, causing great agony. Several studies at our institution show that only a few patients die from local tumor growth when treated according to modern protocols. Likewise, as demonstrated in Table 3, only one patient completing the current treatment protocol died from local relapse in this study. In sharp contrast, a review of 79 ATC patients at our institution showed that about half succumbed to local tumor growth from 1930 – 1970\(^30\). During this time period, a single modality treatment of either radiotherapy or surgery was used.
Among those not completing the treatment protocol in this study, more than half died from local tumor growth, further elucidating the value of aggressive treatment. Also, survival expectancy was significantly lower in this group, as shown in Figure 3, although this probably reflects a selection bias toward medically favorable patients.

Earlier publications have identified several factors as prognostic to superior survival outcome. Such prognostic factors include absence of distant metastases at diagnosis, age and extrathyroidal invasion. Analysis of these variables showed no impact on survival in this study.

For future management of ATC, it is important to determine whether ATC develops from a pre-existing WDTC, arises de novo or if both are possible. If ATC actually is a transformation from a WDTC, the dedifferentiation process needs to be fathomed and potential molecular targets for new drugs identified. The fact that ATC cell lines with TP53 mutations redifferentiates when wild type TP53 is reintroduced, suggests that gene therapy might have a role in future treatment.

In conclusion, considerable progress in achieving local control of this lethal malignancy of the thyroid gland has been obtained over the past decades. Unquestionably, this is of great importance to both patients and relatives. Nevertheless, survival has not changed, necessitating further understanding of the underlying mechanisms of tumorigenesis.

REFERENCES

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