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Review Article

Anaplastic (undifferentiated) thyroid cancer: improved insight and therapeutic strategy into a highly aggressive disease

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Abstract

Background: This review article discusses the clinical and diagnostic implications of anaplastic thyroid cancer, recognizing the aggressive nature of the disease and extensive disease progression upon diagnosis. Standard treatment strategies (surgical, chemotherapy, radiation) are discussed, comparing adjuvant and neo-adjuvant regimens and the emergence of tumour resistance with expression of multidrug resistance pumps. We question the pathological evolution of anaplasia as a 'de novo' disease or a post malignant transformation or dedifferentiation and the therapeutic implications of p53 mutation. Future treatment options are reviewed with an emphasis on specific molecular targets responsible for the neoplastic phenotype.

Method: An electronic search on Medline and Pubmed was performed under 'anaplastic thyroid carcinoma', 'anaplastic thyroid carcinogenesis', 'anaplastic thyroid carcinoma treatment reviews'. Relevant papers were systematically reviewed from 1965 to present.

Key words: Thyroid Gland; Anaplastic Cancer; Cancer Chemotherapy Protocols

Introduction

Anaplastic thyroid carcinoma (ATC) is a rare neoplasm which holds a dismal prognosis. Fortunately the worldwide incidence of ATC has decreased.[1,2] Of the estimated 1460 deaths from thyroid cancer in 2004 in the United States, over half were directly due to the anaplastic variant.[3]

ATC is uncommon, representing 2 per cent of all thyroid cancers with a mean survival of three to seven months after diagnosis, with a five-year survival of 1–7.1 per cent.[2,4–9] Such is its biological aggression that tumour doubling time has been reported in one week.[10]

The histological types of thyroid cancer include papillary, follicular, hurtle, medullary and anaplastic carcinoma. Papillary, follicular and hurtle cell are considered well differentiated; however, anaplastic is a poorly or undifferentiated carcinoma. The histological appearance is highly variable. There are three histologic patterns of ATC, i.e. large cell, spindle cell and small cell variants. Gross appearance is a hard grey-white tumour. The tumour invades arteries and veins, occluding them while producing foci of infarction within itself. Although there is variation within the microscopic classification of the disease, pathologic subtypes have identical clinical behaviours and have no differing prognostic significance. ATC can be considered as a single entity.[4] Improved immunohistochemical techniques have revealed that the majority of small cell cancers are non-Hodgkin lymphoma of the thyroid, 'insular' variants of follicular, or medullary carcinoma.[11,12]

Diagnosis

ATC presents in an elderly population, mostly in the sixth to seventh decades of life, marked by pain, dysphagia, hoarseness and occasional dyspnoea with extensive local invasion of surrounding tissues. Ninety per cent of patients have direct invasion of adjacent structures such as the peri-thyroid fat, trachea, oesophagus, vasculature and muscles. Distant foci of tumour are seen in 20–50 per cent of

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patients. The most common sites of metastases are the lungs in 80 per cent, bone in 6–15 per cent and brain in 5–13 per cent.[11,13] Fine needle aspiration of a solitary thyroid nodule is the investigation of choice for suspicious neck lumps, with ultrasound and CT scanning of the neck and chest. A solitary nodule over 3.0 cm has a 30 per cent incidence of malignancy.[14] Death is attributed to upper airway obstruction and suffocation in half of patients, and to a combination of complications of local and distant disease, therapy (or both) in the remainder.[15] Although the mean survival is approximately three to seven months, the most important prognostic factor is the amount of disease present at the time of diagnosis.[5,16,17]

Current therapeutic strategies

The management of ATC has evolved from aggressive surgical intervention to alternatives to combination therapeutic options. Improved insight into molecular, genetic and biochemical changes occurring during the process of carcinogenesis have changed the focus of drug development from empirical therapy towards therapies acting at specific molecular targets which are responsible for the neoplastic phenotype.

Surgery

It is agreed in the literature that only combination therapeutic strategies will afford an improvement in survival statistics.[18–23] The extent of surgical resection of ATC remains controversial. The locally invasive nature of ATC often results in incomplete resections.[24] Furthermore, as up to 50 per cent of patients on presentation have distant metastases,[11,13] palliative resection may be the only viable option. Total thyroidectomy is only justified if mediastinal and cervical disease can be completely removed with limited morbidity.[25,26] The role of extended resection including pharyngo-oesophagectomy and total laryngectomy is open to debate.[21,27] No effective surgical treatment is available for distant metastases of ATC.

The Mayo Clinic recently published an ominous account of the last 50 years of surgical experience with ATC. They found no survival advantage between radical and marginal resection.[12] However, a survival advantage (two versus six months) has been reported with macroscopic clearance.[28] The integration of chemotherapy into the radiotherapy and surgical formula also improved survival. The order of therapeutic strategy is now the focus of research and debate.[19,29]

Surgery/radiotherapy

Results of retrospective series of treatment of ATC with radiotherapy alone, or post surgery, are conflicting, although they appear to suggest that higher doses of radiotherapy are associated with improved survival.

A Dutch review by Pierie[30] of 67 ATC patients revealed a survival advantage relating to extent of surgery and radiation dose. Surgery was performed in 44 of 67 patients, with 12 complete resections. The six-month and one and three-year survival rates were 92 per cent, 92 per cent and 83 per cent after complete resection; 53 per cent, 35 per cent and 0 per cent after debulking; and 22 per cent, 4 per cent and 0 per cent after no resection, respectively ($p < 0.0001$). A radiation dose of > 45 Gy improved survival as compared with a lower dose ($p = 0.02$). Multivariate analysis showed that age ≤ 70 years, absence of dyspnoea or dysphagia at presentation, a tumour size ≤ 5 cm, and any surgical resection improved survival ($p < 0.05$). Of course the extent of surgery relating to a survival advantage is not confirmed by other retrospective reviews.

Levendag *et al.*[31] reported on 51 patients treated with palliative radiotherapy with or without chemotherapy. This showed similar results, indicating that radiotherapy in excess of 30 Gy improved survival (3.3 versus 0.6 months for those receiving < 30 Gy). A survival advantage was also observed for those who completely responded to radiotherapy over those with a partial response (7.5 versus 1.6 months), a common observation in these reviews. However, some patients who achieve local control will die shortly after treatment due to metastatic disease.

A series from the Beatson Oncology Centre in Glasgow[25] did not show a survival advantage for radiotherapy, despite an 80 per cent response rate.

Chemotherapy

The majority of ATC patients develop metastases during their illness. Hence there is clearly an essential role for systemic chemotherapy. Doxorubicin has been the most commonly reported drug, but monotherapy has been shown to have less than 20 per cent response rate, with no complete responses. The addition of cisplatin to doxorubicin has modestly improved response rates.[25,26]

A phase II trial by Ain *et al.*[32] from the Veterans Affairs Medical Center, Lexington, Kentucky reported a 53 per cent response rate with the single agent paclitaxel. Twenty patients with persistent or metastatic ATC were treated with 96-hour continuous infusion paclitaxel every three weeks for one to six cycles. This regimen was well tolerated, although grade 3 peripheral neuropathy was experienced with some schedules. Median survival of responders was 32 weeks, although that of the non-responders was only seven weeks. There was one complete response.

Yeung *et al.*[33] at MD Anderson found that the addition of manumycin (a farnesyl:protein transferase inhibitor) *in vitro* enhanced paclitaxel cytotoxicity.

German investigators[34] have researched cisplatin and gemcitabine alone or in combination in ATC cell lines. Gemcitabine monotherapy showed promising cytostatic activity, enhanced by the addition of cisplatin. Their interaction was schedule- and dose-dependent, favouring a regimen in which gemcitabine is followed by cisplatin. DNA synthesis

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inhibition and S phase arrest may be important determinants for this drug interaction.

A National Cancer Institute trial[35] of induction doxorubicin/cisplatin followed by combretastatin A4 phosphate and radiotherapy for newly diagnosed regionally advanced ATC is accruing. Combretastatin A4 phosphate (CA4P) represents the lead compound in a group of novel tubulin depolymerizing agents being developed as vascular targeting agents. Preclinical studies have shown that CA4P induces blood flow reductions and subsequent tumour cell death in a variety of preclinical models.

Surgery/chemo-radiotherapy

Heron *et al.*[36] at the University of Pittsburgh demonstrated a survival advantage using hyperfractionated radiotherapy and chemotherapy compared to conventional radiotherapy alone. Thirty-two ATC patients treated over a period of five decades were analysed. A variety of radiotherapy techniques was used. Chemotherapy consisted of doxorubicin, paclitaxel, vincristine or cisplatin. Among patients with ATC surgery, hyperfractionated radiotherapy in conjunction with chemotherapy was associated with better survival but not progression-free survival compared with conventional radiotherapy.

Doxorubicin enhances radiotherapy toxicity, and it is unusual to instigate concomitant therapy at standard doses. Simpson *et al.*[37] devised a protocol of hyperfractionated radiotherapy, administering a small number of large radiation fractions (350–800 rads) with concomitant doxorubicin. Local response was good, although toxicity was unacceptable. Two patients died of spinal cord necrosis and a third of pneumonitis.

Kim and Leeper[22] at Memorial Sloan-Kettering modified Simpson's approach. Nineteen patients with anaplastic giant and spindle cell carcinoma of the thyroid received doxorubicin (10 mg/m^2, a low dose) once weekly before hyperfractionated radiotherapy. Radiation therapy was carried out with a fractional dose of 1.6 Gy per treatment twice a day for three days per week to a total dose of 57.6 Gy in 40 days. Despite an initial complete tumour response rate of 84 per cent, median survival was only one year. Unlike Simpson's data, no disproportionately enhanced normal tissue morbidity was seen.

Neo-adjuvant versus adjuvant chemo-radiotherapy

Between 1984 and 1999, 55 consecutive ATC patients at the Lund University Hospital in Sweden[38] were prospectively treated with hyperfractionated radiotherapy, doxorubicin, and surgery when feasible. Radiotherapy was delivered at 1.0–1.6 Gy twice a day, to a total dose of 46 Gy. Some patients received all radiotherapy prior to surgery, and some as a split course, 30 Gy pre-operatively and 15 Gy post-operatively. Surgery was performed in 40 patients. No patient failed to complete the protocol due to toxicity. Death was attributed to local failure in only 13 cases (24 per cent). Five patients (9 per cent) lived more than two years. Results were best for the entire pre-operative 1.6 Gy twice a day regimen. Seventeen of 22 did not recur locally. Of those who proceeded to surgery in this group, none failed locally.

A total of 162 patients with ATC treated at the Institute of Oncology, Ljubljana[39] have been studied. There was no difference in one-year survival between patients who underwent surgical resection followed by chemo-radiotherapy, compared to neo-adjuvant chemotherapy, radiotherapy or chemo-radiotherapy. It is interesting to note that the primary chemotherapy or radiotherapy group was composed of older patients, with faster growing, larger tumours. Despite this, survival was the same, 50 per cent were alive in one year.

Anaplastic carcinogenesis

Whilst the carcinogenesis progression of several cancers has been elucidated, in particular that of colon cancer, a progression model for thyroid carcinogenesis has not been defined. Furthermore, thyroid tissue undergoes molecular and genetic alterations, provoking transformation from normal tissue to adenoma and from differentiated to undifferentiated carcinoma. It is generally accepted that this transformation proceeds through multiple discrete steps, as a single oncogenic mutation cannot induce malignant transformation on its own. It is unclear if ATC can arise *de novo*. Furthermore there is no evidence to suggest that malignant transformation is a structured and predictable process.[40]

The transformation model of anaplastic tumorigenesis, or post-malignant transformation progression, stems from pathologic observation of anaplastic tumours with a differentiated carcinoma component.[6,41–45] An association has been established between the aggressive histologic subtypes of papillary carcinoma (insular and tall cell) with ATC and with the hypothesis that they represent intermediate forms in the 'transformation' process.[42,45–47] However, one institution's 50-year experience found no evidence of a differentiated carcinoma component within their anaplastic population.[12] Investigation of the DNA content of 11 ATC and adjacent differentiated carcinoma found all anaplastic tumours to be aneuploid, but only seven of the 11 differentiated carcinomas were diploid, thus lending further credence to the *de novo* hypothesis.[48]

Thyroid tumorigenesis is complex, involving several cell cycle regulators, oncogenes, growth hormones and cellular differentiation and adhesive compounds. Early stages of thyroid cancer development may be related to growth factor receptors or proto-oncogene activation *(ret, mes, ras)*.[49] Neoplastic expression of these genes is related to follicular *(ras)* and papillary *(met, ret)* carcinoma. Mutation of tumour suppressor genes such as p53 or Rb is observed in poorly differentiated carcinoma. Mutations of p53 are considered to be late events in the sequence of human carcinogenesis.[40,50,51] p53 is a tetrameric nuclear phosphoprotein transcription

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factor which is the product of the TP53 gene. p53 is a tumour suppressor protein that acts in the nucleus to effect cell cycle arrest and apoptosis. p53 is mutated or absent in approximately half of all human cancers including lung, colon and breast;[52–55] 52 per cent of ATC have shown TP53 or p53 mutation.[46] These mutations are rarely found in papillary or follicular carcinomas, although genomic instability is present.[6,56] p53 mutations are thought to be associated with reduced chemosensitivity and radiosensitivity.[57,58] p53 mutation lies at the heart of the anaplastic tumorigenesis debate. Either the mutation allows for accelerated genomic instability or loss of wild-type p53 results in growth, angiogenesis and the development of the anaplastic undifferentiation, hence anaplastic tumorigenesis.[57–59] It is well documented that the re-introduction of wild-type p53 into ATC cells results in the induction of differentiation, inhibition of cellular proliferation, restoration of cellular responsiveness to physiologic stimuli (thyroid stimulating hormone) and re-expression of thyroid peroxidase.[59–61] The introduction of TP53 gene therapy using adenovirus may serve as a significant adjunct to standard chemotherapy in management of this disease.[62]

Multidrug resistance

In recent years tumour resistance of a number of cancers to chemotherapy has further complicated effective treatment outcomes. This is due to the expression of the multi-drug resistant protein. Multi-drug resistance (MDR) was first described as a 170-kDa P-glycoprotein (P-gp) pump which can displace common cytotoxic drugs including anthrocyclines, some vinca alloids and xenobiotics.[63] Investigations into these pumps have led to the development of many agents used to negate the pump action. Recent work on non-steroidal anti-inflammatory drugs (NSAIDs) shows inhibition of the MRP-1 protein in a variety of cancer cell lines with a number of differing NSAIDs including sulindac, mefanamic acid and indomethacin.[64,65] The MRP-1 protein is expressed in anaplastic thyroid cancer[66,67] and further research is required to investigate its inhibition offering synergistic chemotherapeutic potential.

Future chemotherapeutic strategies

In recent years the significance of apoptosis of tumour growth has been recognized. Now it is clear that decreased rates of apoptosis contribute as much to growth as proliferation. This department recently proposed that vascular endothelial growth factor (VEGF) promotes neovascularization but also acts as a survival agent for tumour cells, protecting them from apoptosis.[68] Promotion of apoptosis is emerging as an important treatment strategy. The aforementioned NSAIDs have been implicated in increasing apoptosis levels and decreasing concentration levels of VEGF *in vitro* and *in vivo*.[69]

Anti-angiogenic agents, in particular those directed against VEGF, have multiple anti-tumour effects. These therapies have also been shown to increase the efficacy of conventional chemotherapy and radiotherapy. ATC markedly expresses VEGF compared with normal thyroid tissue and this overexpression is associated with the development of a highly malignant human phenotype.[70–72]

Several chemotherapeutic agents have been introduced as novel anticancer drugs for tumours with mutant p53. 17-Allylamino-17-demethoxygeldanamycin (17-AAG) is a derivative of geldanamycin, a benzoquinone ansamycin antibiotic which binds to Hsp90 (heat shock protein 90) and alters its function.[62,73–80] Hsp90 client proteins play important roles in the regulation of the cell cycle, cell survival, cell growth, oncogenesis and apoptosis.

17-AAG binds with a high affinity into the ATP binding pocket in Hsp90 and induces the degradation of proteins that require this chaperone for conformational maturation. The ubiquitin (Ub)-proteasome pathway is the major non-lysosomal proteolytic pathway in the body. This is a degradation pathway for medium-sized proteins including wild-type p53. Proteins are covalently bonded to the 76 amino acid protein ubiquitin. This results in the breakdown of the protein via the 26 S proteasome which is a large proteasome complex. Wild-type p53 transcriptionally induces Mdm-2, an oncogene which interacts with p53 affecting either cell immortalization or death, thereby targeting itself for protease degradation. Mutant p53 does not induce the Mdm-2 and is therefore not degraded, instead it is overexpressed. Geldanamycin causes the degradation of mutant p53.[81] Inhibition of Hsp90 leads to depletion of mutant p53, but not wild-type p53 in leukaemia, breast and prostate cell lines. Geldanamycin restores polyubiquitination and degradation of mutant p53 by the proteasome.[82,83]

17-AAG is a less toxic analogue of geldanamycin, inducing apoptosis and displaying anti-tumour effects. In a Phase I trial at Memorial Sloan Kettering, the drug was administered daily for five days at 80 mg/m^2 with peak plasma levels of 2700 nM. The infusion was repeated every three weeks. The toxicities noted were diarrhoea, thrombocytopenia and transient transaminitis.[84] At the Royal Marsden Hospital in the UK, with weekly administrations at doses of 80 mg/m^2, no biochemical or haematological toxicities were observed.[75,85] Further trials are required to analyse the effects of this potential therapy on ATC.

Conclusion

Anaplastic thyroid carcinoma remains a highly aggressive lethal disease whose origins remain controversial. Does ATC arise *de novo* or is it part of a de-differentiation, post malignant transformation? The cellular processes governing these mechanisms remain unknown and with continued research offer future therapeutic potential.

Despite reports of adequate local control, survival with multimodal therapy remains poor. A common observation in combination therapy reviews is that a small cohort of complete responders have significant

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survivals, thus emphasizing the need to treat appropriate patients adequately. Neo-adjuvant chemo-radiotherapy may be superior to adjuvant therapy. Systemic chemotherapy outside multimodality therapy should be confined to clinical trials.

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