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NOVEL APPROACH IN ANAPLASTIC CARCINOMA OF THYROID –IS THERE LIGHT AT THE END OF THE TUNNEL?

Oncology

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ABSTRACT

BACKGROUND: Anaplastic thyroid carcinoma (ATC) is a rare, lethal type of thyroid cancer. The paucity of data has eluded the formation of standardised treatment protocols. A multi-modality approach is adopted and for patients desiring aggressive treatment, radical surgery along with chemoradiation is advocated. Patients with metastatic ATC are encouraged to participate in clinical trials as no definitive treatment is available.

CASE SUMMARY: We present a case of an elderly patient who presented in an advanced stage of ATC with distant metastasis. The patient received the entire gamut of treatment available and responded well. The patient was decannulated and no longer PEG-tube dependent.

CONCLUSION: Though treatment for ATC remains an enigma but the novel treatments offers a ray of hope in this disease with historically miserable prognosis.

KEYWORDS

Anaplastic carcinoma, Thyroid cancer, Cyberknife in thyroid cancer, Metronomic therapy in thyroid cancer,

INTRODUCTION:

Anaplastic thyroid carcinoma constitutes only 2% to 5% of clinically recognised thyroid cancers. However, they are responsible for more than 50% of deaths attributed to thyroid cancer [1,2]. The median survival is poor ranging from 3-10 months despite aggressive multi-modality treatment. Survival rates at 1 year were 72.7%, 24.8%, and 8.2% for patients with disease stage IVA, IVB, and IVC, respectively. Most patients present in loco-regionally advanced stages. Approximately 40% of patients have palpable low-neck metastases and 20–50% present with distant metastases at diagnosis [2,3]. Owing to the rarity of the disease, there is lack of data to support a standardised treatment [4,5,6]. Trimodality therapy (surgery, radiation and chemotherapy) in patients without distant metastases appears to maximize local-regional control and survival [7].

The management of thyroid cancer calls for a multi-modality approach. Considering the dismal prognosis of the patient and lack of consensus regarding the ideal treatment, patients must be involved in the decision making process. The ideal treatment if the disease is loco-regionally resectable is surgical excision. However, the aim in all such cases would be to achieve negative margins (R1 resection) .In cases where distant spread has occurred, the aim of surgical resection may be only to prevent airway or oesophageal obstruction. In cases of non-metastatic ATC where the patient is keen of aggressive approach , a combined modality of treatment with cytotoxic chemotherapy and radiotherapy can be offered. The chemotherapeutic drugs that can be used is some combination of taxane (paclitaxel or docetaxel), and/or anthracyclines (doxorubicin) and/or platin (cisplatin or carboplatin) . In advanced disease with metastasis, the data available is meagre and standardised treatment protocols are lacking. If the patient is desirous of aggressive therapy , inclusion in clinical trials is advocated .If aggressive therapy is not feasible or not desired by the patient , best supportive care at home should be provided as an alternative treatment [8].

This report revolves around an elderly gentleman, who presented to us in an advanced stage of anaplastic carcinoma. The patient was explained about the disease outcome and the various treatment options available. He was also explained about the paucity of data regarding the ideal treatment and was actively involved in the decision making-process.

CASE HISTORY:

A 72-year-old gentleman presented with swelling in front of neck of 3months duration in Feb,2016 . He had initially presented with the above complaints to a secondary care centre where initial investigations were carried out . Subsequently, he presented to our centre to seek a second opinion. The ultrasound guided FNAC of thyroid was reviewed at our centre and possibilities of 1) Anaplastic carcinoma 2) Secondary involvement of thyroid by a head and neck carcinoma was suggested. FDG PET CT Scan done subsequently showed (3.4 x 3.1 x 4 cm) ill-defined metabolically active hypodense mass involving the lower pole of left lobe of thyroid, extending inferiorly & posteriorly into the left trachea-esophageal groove and left paratracheal regions with infiltration of left lateral wall of trachea , a (2.2 x 2 x 3.6 cm) metabolically active hypodense lesion along the right lateral wall of mid esophagus, likely representing metastatic para esophageal lymph node and a (1.3 x 0.9 cm) metabolically active nodule in the left adrenal gland, likely metastasis. His diagnosed was confirmed as anaplastic carcinoma of thyroid (c T4a N1a M1, Stage IVC).

The prognosis, outcomes and various treatment options available were elaborately discussed with the patient. Owing to the advanced stage of the disease, the patient was offered radiation therapy and/or systemic therapy. However, the patient desired for alternative treatment at home. After a detailed discussion with the patient regarding the available treatment options and their palliative nature, the patient was started on metronomic therapy. The Metronomic therapy was delivered as a four-drug regimen – Tab Methotrexate (30mg weekly), Tab Geftinib (250mg once daily), Tab Celecoxib (200mg once daily) and Tab Metformin SR (500mg once daily). Following treatment, patient showed improvement of symptoms. Patient received Activated T-cells with 57 X 10 ^ 6 Total cell count and 99% viability, measuring 4 ml infused over 1 hour after diluting it with 100ml NS on 18-04-16. PET CT done on 13-05-16 (Figure 1) showed relatively stable ill-defined metabolically active hypodense mass involving the lower pole of left lobe of thyroid and mild regression of metabolically active hypodense lesion along the right lateral wall of mid oesophagus.He received 2nd week Activated T-cell transfusion on 09-06-16. PET-CT done on 23-06-16 showed progression of disease in neck and left adrenal gland . In view of the impending stridor, Patient underwent elective tracheostomy and feeding jejunostomy on 27-06-16. He received Cyber knife Robotic Radiosurgery (30Gy/5# to neck-thyroid from 01-07-16 to 05-07-16; 30Gy/5# to Left adrenal metastasis from 18-07-16 to 22-07-16). He also received EBRT using IG-IMRT technique from 31-08-16 to 28-10-16(60.2Gy/28# to GTV, 56Gy/28# to GTV Primary, 50.4Gy/28# to CTV and 56Gy/28# to nodes; sites treated neck and mediastinum). He was on 2 months of Tab Pazopanib starting from 28-10-16. On 25-11-16, he was decannulated. PET-CT done subsequently showed interval development of metabolically active intrahepatic lesions. USG guided core biopsy from the liver lesion with immunohistochemical examination (Figure 2A , B , C) confirmed metastasis from anaplastic carcinoma of thyroid. PET-CT done on 12-04-17 showed progressive disease in neck with infiltration of cervical oesophagus and posterior tracheal membrane and liver metastasis. He received 1st cycle of 1st week and 1st cycle of 2nd week of chemotherapy with Inj Mitotax 120 mg . In view of his improving symptoms and ability to take orally, FJ was removed on 26-04-17.He completed 3rd cycle of 3rd week of chemotherapy..

He was admitted in the hospital for hypotension and generalised weakness on 23-08-17. However, inspite of the long and worthy journey of approximately 1year 6 months that he undertook post diagnosis , he succumed to his disease

DISCUSSION:

ATC is a rare type of thyroid cancer with dismal prognosis. ATC patients have a median survival of 5 months and a 20% 1-year survival rate [9]. Despite aggressive multi-modality treatment, the survival rates are poor. The lack of comprehensive data given the rarity of the disease makes it difficult to have standardised treatment protocols for these patients. A definite diagnosis of ATC by morphological studies and appropriate immunostaining is necessary to exclude less aggressive and treatable entities that mimic ATC. The radiological staging involves the use of cross-sectional imaging including neck ultrasound, CT scans or MRI (for the neck and chest), and PET/CT fusion scans. All ATCs are stage IV. Stage IVA lesions are intrathyroidal (T4a), and N0, M0 (no distant metastases). In stage IVB, the primary tumour has gross extra thyroidal extension, any N, M0. Stage IVC patients have distant metastases. A multi-modality treatment with a detailed discussion with the patient needs to be planned .The primary modality of treatment is surgical resection if loco-regional disease is present and grossly negative margin (R1 resection) can be achieved. The mainstay of therapy in addition to surgery can involve loco- regional approaches, most commonly radiotherapy (but sometimes also interventional radiological approaches), and systemic approaches, most commonly cytotoxic chemotherapy (but sometimes also novel targeted therapeutics). However, no systemic therapeutic of proven benefits in terms of improved survival and/or quality of life in advanced ATC have been identified [8].Therefore, such patients who desire aggressive treatment are either enrolled into therapeutic clinical trials or in absence of suitable trials are given the option of available therapeutics in a non-study setting.

Our patient, who presented to us at an advanced stage of ATC, was explained in details about the disease, the dismal prognosis and the treatment options available. He preferred a palliation treatment at home rather than the aggressive modalities available. In view of the patient's desire, metronomic chemotherapy was offered to him. Metronomic therapy, which essentially refers to the schedule, which consists of chronic, equally spaced, and (generally) low doses of various chemotherapeutic drugs without extended rest periods in contrast to “maximal tolerable dose” employed in usual treatment protocols. The anti-tumour activity of metronomic therapy has been attributed to its anti-angiogenic action, inhibition of circulating endothelial progenitor cells, direct cytotoxicity and stimulation of immune response [10,11,12,13]. The depletion of T-reg cells (CD4+CD25+) by metronomic chemotherapy allows the cytotoxic (CD8) and helper (CD4) T-lymphocytes as well as natural killer cells to act unhindered in staging an antitumor immune response [14,15].

As our patient showed improvement in symptoms ,he was motivated to continue further treatment . However, he refused treatment by conventional modalities (radiation and chemotherapy) . Hence, he was offered Immunotherapy with Autologous lymphocyte cell implantation procedure to which he agreed. He received 2 cycles of activated T-cells.The patient responded well and the follow-up PET-CT showed a stable hypodense lesion in the left lobe of thyroid and regression of the hypodense lesion along the right lateral wall of mid-oesophagus.

The patient , however, was tracheostomised in the initial stage despite conventional teaching which promotes tracheostomies and intubation in late stages. Subsequently , he was motivated for further management and he agreed to undergo radiation and chemotherapy.As he had difficulty in swallowing and treatment with chemoradiation therapy was planned, per-cutaneous gastrostomy for enteral nutrition was done [16].

There are very few reports of thyroid cancer, even anaplastic thyroid cancer, metastasizing to the adrenal [17]. Several studies have reported that Stereotactic body radiation therapy (SBRT) can be safely delivered in single fraction, or hypo fractionated, regimens for the treatment of adrenal metastases [18]. Torok et al in a retrospective study reported an actuarial local control of 63% at 1 year of adrenal tumours subjected to SBRT [19]. In view of the presence of adrenal metastasis in the patient, Cyberknife radiosurgery was given to both the neck and the adrenal metastasis.

Definitive radiation therapy and chemotherapy are recommended for patients with locally advanced unresectable disease. Fractionation regimens vary from hypo fractionation (dose per fraction ≥2.5Gy) for palliation to hyper fractionated acceleration (>5 fractions per week and reduced overall treatment time) with chemotherapy [20,21,22]. It is important in such patients to deliver the highest dose of radiation possible without causing injury to the surrounding normal tissues, eg, spinal cord. This is easily achieved with targeted radiation techniques such as IMRT. Furthermore, image-guided IMRT (IG-IMRT, or commonly known as IGRT) can improve the precision of radiation delivery by capturing real-time positional films of the treatment volume during radiation delivery [23]. The patient received EBRT using IG-IMRT technique to the primary in neck and mediastinum.

Pazopanib had shown promising anti-neoplastic effect in multiple DTC cell lines in-vitro, it was assumed it would have therapeutic role in advanced ATC. Pazopanib, however, demonstrated only minimal activity in human ATC within the context of the multi-instituitional Phase 2 trial [24]. In a study by Crescent et al Pazopanib/paclitaxel combination was found to be a promising candidate therapeutic approach in ATC [25]. The patient was given Pazopanib orally for two months in combination with 3 cycles of 3 weeks of chemotherapy.

CONCLUSION:

To conclude, possibly a combined modality with use of newer novel treatments is the way ahead in treatment of this type of deadly cancers.

The take home messages from this case are

1. Despite dismal outcomes in metastatic ATC, these multimodality novel treatments improve the quality of life prompting the need to revisit the treatment of these deadly cancers.
2. An elective tracheostomy done early may improve quality of life (QOL) contrary to the conventional teaching of a late tracheostomy or intubation in advanced ATC. Even in metastatic ATC with grave prognosis, decannulation is feasible and not a myth.
3. The combination of activated T-cell infusion and Cyber knife treatment needs to be further explored.
4. The perspective of the patient and patient's relatives needs to be taken into account and all attempts to improve the QOL even if it means adding few worthy days should be undertaken.

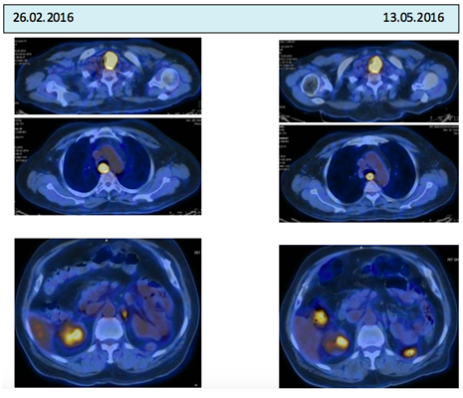

Figure 1 :The comparative PET/CT fusion images showing stable lesion in Left lower lobe of thyroid ,mild regression of the mass around the oesophagus and regression of the nodule in left adrenal gland.

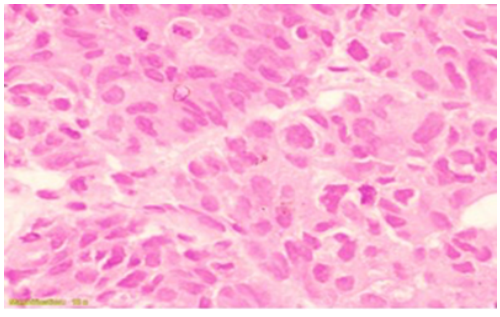

Figure 2(A)- Haematoxylin and eosin-of liver biopsy showing poorly differentiated Cells with ovoid to spindle nucleus, mitoses are seen.

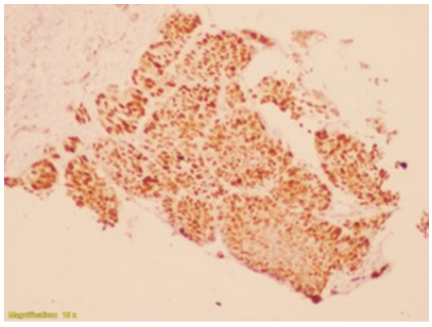

Figure 2(B): P53 stain of Liver Biopsy showing strong nuclear positivity.

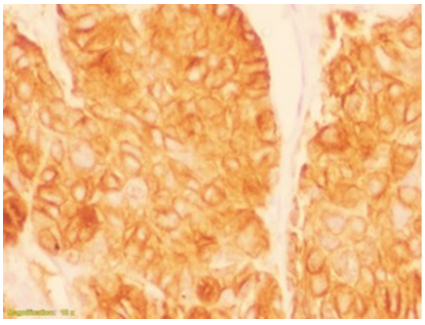

Figure 2(C): Pan Cytokeratin stain of Liver Biopsy: Strong cytoplasmic and membranous stain. Features are suggestive of metastatic poorly differentiated carcinoma

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