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Lenvatinib in Metastatic DTC (Differentiated Thyroid Cancer)- A Pragmatic Approach with Dosing

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Abbreviations: RR-DTC: Radio iodine refractory Differentiated Thyroid Cancers

Introduction

Thyroid cancer has become one of the fastest-increasing cancers in recent years. There are nearly 300,000 new cases of thyroid cancer annually and approximately 40,000 people die from thyroid cancer worldwide each year [1]. Differentiated thyroid cancer is a highly treatable and curable cancer (DTC). 90% of the patients with DTC will be alive at 10 yrs after the diagnosis. However, in patients who develop radio iodine resistance these survival rates are reduced down to 10% over the same period [2-4]. After a long struggle of finding a suitable alternative to largely ineffective treatment with chemotherapy, Multikinase Inhibitors Sorafenib and Lenvatinib after demonstrated success in Decision [5] and Select [6] trials respectively, have gained FDA and EMA approval for the treatment of Radio iodine refractory Differentiated Thyroid Cancers (RR-DTC).

Although effective, these agents as a class effect carry a considerable toxicity profile. In both the registration trials, a significant portion of patients required dose modifications in order to maintain compliance and tolerability. Common toxicities of fatigue, hypertension, palmoplantar effect diarrhoea and weight loss of more than 10% and proteinuria played a common theme effecting majority of the patients. In the SELECT trial 67.8% of the patients required dose modifications and although the intended dose was 24mg, median dose was calculated at 17.2 mg. The time for first dose reduction was observed at 3 months. We present a real time experience of cases with RR DTC treated with Lenvatinib at our facility that fall outside of the spectrum of patients recruited to the trials as above. In view of rapid onset of toxicities or co morbidities we initiated the treatment at a dose of 14mg which proved to be reasonably well tolerated and effective with demonstrable clinical responses within 1 month of initiation of treatment.

Case 1

Patient is a female of 67 yrs of age. She has significant co morbidities of moderate obesity and long standing Diabetes controlled on oral hypoglycaemic. She is also a long standing hypertensive controlled on 2 anti-hypertensive agents. She has osteoarthritis and hence requires assistance with activities of daily living. She presented with right neck swelling in 2013 and underwent total thyroidectomy with neck dissection. Pathology confirmed PTC T3 N2 M0 with extra capsular spread. She had multiple doses of radio iodine due to persistent residual disease in the neck. In 2016 she was restaged due to progressive neck disease that was negative on radio iodine scan. Her staging CT confirmed bilateral neck nodes. She underwent neck dissection followed by external beam radiation but within 3 months she had further recurrence in the neck. Restaging also confirmed bilateral lung metastasis. She was initially started on Sorefanib. She presented within 3 days of start of Sorefanib at recommended doses of 400 mg twice daily. She refused to be re-challenged with Sorafenib even with dose modification. We then proceeded with Lenvatinib at 14 mg (instead of 24mg due to toxicity concerns) which she tolerated reasonably well with problems with occasional headache and grade 2 fatigues. No problems with hypertension were observed. She demonstrated a clinical response within 4 weeks of initiation of treatment with reduction in size of neck nodes to half. She continues on Lenvatinib waiting restaging.

Case 2

71yrs old lady with no known co morbidities. Resident of the southern region of KSA. She was diagnosed with DTC, Insular variant of papillary thyroid carcinoma, in 2007. She had had multiple surgeries and radio iodine ablative doses since 2007. Patient re-presented in 2016 Dec with a mass in the left thyroid bed invading into the trachea. No distal metastasis was observed. She proceeded to have external beam radiation after refusal to undergo surgery. Following radiation she underwent restaging CT and PET which showed intense tracer uptake in the tumour with minimal change post radiation. Due to the critical position of the tumour that was active even after radiotherapy, treatment with Lenvatinib

was contemplated and patient commenced on 14mg dose. Reduced dose was considered because of the risk of rapid response on Lenvatinib and fistulation. She was reviewed in clinic after 2 weeks. She complained of grade 2 fatigue and anorexia but nil else. There was already a clinical response observed in palpable disease in the neck. Due to distance needing to travel, patient does not wish frequent visits and hence will be managed with phone follow up and clinic visits every 3 months.

Case 3

65 yrs old female patient, resident from North east of KSA presented in 2010 after having had total thyroidectomy for papillary thyroid cancer. She had radio iodine ablation repeated twice due to persistent uptake of radio iodine in the neck. Patient on follow up was noted to have no uptake in the neck but persistently raised thyroglobulin levels despite fully suppressed TSH. In 2014 she underwent a CT scan and PET confirming lung metastasis. She was started on Sorafenib, 400 mg twice daily in 2014. She remained on it for 2 years with stable disease when her thyroglobulin was noted to be on the rise in 2017. Her CT scan confirmed progression in the lung. She was then started on Lenvatinibat 24mg. She presented after 4 days after commencing Lenvatinib with PV bleed. Gynaecology review did not reveal any cause for the bleed. After resolution of the symptoms she was recommenced on Lenvatinib. She represented after a week with grade 3 fatigue and generalised aches. The Lenvatinib dose was reduced to 14mg. She tolerated this dose well and CT and PET after 6 weeks of treatment showed reduction in the SUV max and size of the lesions in the lung.

Discussion

We have presented our experience of treating patients over the age of 65 yrs with poor prognostic RR DTC. It is important to note that of 261 patients who received LENVIMA in the Pivotal Phase 3 SELECT trial, 118 (45.2%) were ≥65 years of age and 29 (11.1%) were ≥75 years of age. Subjects 75 years or older had a higher incidence of fatal AEs. Compared with subjects younger than 65, subjects who were 75 years or older were also more likely to experience (in descending order of frequency) Grade 3-4 hypertension, proteinuria, decreased appetite, and dehydration [7]. These patients pose a particular challenge particularly in an environment where majority are living in remote facilities and monitoring of the toxicities and frequency of the visits to tertiary care hospitals is difficult. So what practical arrangements would be suitable to ensure safety of the treatment?

Based on our initial experience and concerns with the rapid toxicities at full initiation dose of 24mg, in the cases presented above, we decided to initiate treatment at 14mg dose with a view to dose escalate to 18 mg and subsequently to 24 mg toxicities permitting. Fortunately, our patients not only tolerated treatment very well but showed a clinical response within 1 months of initiating treatment with Lenvatinib. Despite this dose, patients still demonstrated grade 2 toxicities with fatigue, headaches, asthenia and abdominal pain (at least in one patient). No hypertension or proteinuria has been noted thus far. Our experience in the unique setting of elderly patients with significant co morbidities and residence in remote areas with no immediate access to tertiary care facility dictated a cautious approach towards toxic treatment which has fortunately proven to be effective and tolerable in this setting. We can thus recommend a similar approach in this group of high risk patient who warrant the use of Lenvatinib i.e initiating treatment at at a lower dose with intent to dose escalate as a safer alternative to full dose with de-escalation.

Conclusion

Our case series highlights the practical difficulties of initiating and monitoring toxic treatments in part of the world where facilities are scarce. In our setting most of the treatments are justified and accepted as result of phase 3 trials conducted elsewhere with little or no experience prior. How patients as well as tumours will respond to the medication remains a mystery till initiation of the treatment. Lenvatinib is no exception to the rule. We readily accept the criticism of initiating the treatment with Lenvatinib with an unlicensed dose of 14 mg but any dose from 14 – 20mg as a start dose would fall under the same criticism. We believe that the correct approach would be to consider the approved dose of 24mg as initiating dose as per licence in the patients fitting the trial inclusion criteria. However, patients such as the ones reported in this series would need a more measured approach. Bearing this in mind and the initial experience of the toxicities in elderly patients with co morbidities but encouraging responses observed in all patients at 14 mg dose, we advocate cautious approach with a lower dose initiation and close monitoring. Furthermore, it confirms that 14mg dose is an effective dose and can be administered safely in our patient population.

References

1. World Health Organization: GLOBOCAN (2012) Cancer Incidence and Mortality Worldwide in 2012.
2. Busaidy NL, Cabanillas ME (2012) Differentiated thyroid cancer: management of patients with radioiodine nonresponsive disease. J Thyroid Res.
3. Durante C, Haddy N, Baudin E, Leboullex S, Harti D et al. (2006) Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J ClinEndocrinolMetab 91(8): 2892-2899.
4. Schlumberger M, Brose M, Elisei R, Leboullex S, Luster M et al. (2014) Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol 2(5): 356-358.
5. MS, Nutting CM, Jarzab B, Rossella E, Salvatore S et al. (2014) Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial Brose. Decision investigators Lancet 384(9940): 319-326.
6. Schlumberger M, Tahara M, Wirth LJ, Robinson B (2015) Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372(7): 621-630.
7. Woodcliff Lake NJ (2015) Lenvima (lenvatinib) capsules LENVIMA® (lenvatinib) is a prescription medicine that is used to treat certain kinds of cancer, USA.