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 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).

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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 Lenvatinib at 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 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.

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   LENVIMA® (lenvatinib) is a prescription medicine that is used to treat
   certain kinds of cancer; USA.