S3-SELECTION OF PATIENTS FOR TKI TREATMENT

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Patients with advanced DTC who are refractory to ^{131}I treatment have a life expectancy of 3-6 years and represent a group for whom there is a clear unmet medical need (1). Radioiodine refractory thyroid cancer is not common, with an estimated incidence of four cases per million population year (5% of patients with clinical thyroid cancer, 250 patients per year in France) (2,3). It occurs more frequently in older patients, in those with large metastases or with poorly differentiated thyroid cancer, and in those with high FDG uptake on PET scan (1, 4).

This review proposes a definition for refractory thyroid cancer, and defines those patients who are candidates for treatment with TKIs.

DEFINITION OF REFRACTORY THYROID CANCER

In all patients treated with ^{131}I, treatment efficacy is assessed by functional parameters (serum Tg level during l-thyroxine therapy and following hormone withdrawal or rhTSH injections, and quantitative ^{131}I uptake in metastases on post-therapy WBS) and also by anatomical imaging with CT scan and MRI. Favorable responses are characterized by parallel decreases in tumor volume on anatomical imaging, ^{131}I uptake, and serum Tg levels. In contrast, a decrease in ^{131}I uptake without a decrease in tumor volume denotes the destruction of differentiated cells with high uptake and the persistence of poorly differentiated foci that will progress. These patients should then be considered DTC refractory to ^{131}I treatment, and they fall into six categories:

a) Patients with metastatic disease that does not take-up ^{131}I *at the time of initial treatment.* For these patients there is evidence that treatment with ^{131}I does not provide any benefit. This group includes patients with structurally evident disease with no ^{131}I uptake on a diagnostic whole-body scan (WBS), because in such patients uptake when present on post-therapy scans will not be sufficient to induce benefit (5).

b) Patients whose tumors lose the ability to take-up ^{131}I *after previous evidence of uptake*. This is due to the eradication by ^{131}I treatment of differentiated cells able to take-up ^{131}I but not of poorly differentiated cells that do not take-up ^{131}I. Progression is likely to occur in these poorly differentiated cells

c) Patients with ^{131}I *uptake retained in some lesions but not in others.* This is frequently seen in patients with multiple large metastases as shown by ^{124}I studies on PET scan (6) and by comparing results of imaging modalities (FDG-PET or diagnostic CT scans) with ^{131}I WBS. In such patients, progression is likely to occur in metastases without ^{131}I uptake (in particular when FDG uptake is present) and ^{131}I treatment will not be beneficial (4, 7, 8)

d) Patients with metastatic disease that progresses despite significant uptake of ^{131}I*.* It has been clearly shown that if progression occurs following a course of adequate radioiodine treatment, subsequent ^{131}I treatment will be ineffective (9).

e) *Less clear is the situation for patients with persistent visible* ^{131}*I uptake in all residual lesions who are not cured despite several treatment courses but whose disease does not progress according to RECIST criteria.* For these patients, the probability of obtaining a cure with further ^{131}I treatment is low (1) and side effects may significantly increase, including the risk of secondary cancers and leukemias (10). It is controversial as to whether these patients (particularly after receiving more than 600 mCi of ^{131}I) should be considered ^{131}I-refractory and whether ^{131}I treatment should be abandoned. The decision to continue ^{131}I treatment in such patients is generally based on their response to previous treatment

courses, persistence of a significant level of ^{131}I uptake on the previous post-therapy WBS, low FDG uptake in tumor foci, and absence of side effects.

f) *Finally, there is a subgroup of patients with advanced disease for whom thyroidectomy is not feasible.* In such patients, ^{131}I treatment is usually not administered because ^{131}I is ineffective when the thyroid gland is still present and ^{131}I uptake status cannot be assessed. These patients could be managed as iodine-refractory patients, or if desired, treated with RAI to destroy the thyroid..

TREATMENT OF REFRACTORY THYROID CANCER-ACTIVE SURVEILLANCE (Table 1)
Once ^{131}I treatment is terminated, L-thyroxine treatment is maintained to suppress TSH secretion and focal treatment of metastases is performed whenever needed. This may include surgery, external radiation beam therapy, and thermo-ablation (radiofrequency or cryo-ablation and cement injection). Also, because bone metastases may induce skeletal related events at short term interval (11), bisphosphonate or denosumab treatment may be effective in patients with bone metastases.

Active surveillance includes a FDG-PET/CT scan or a CT scan of the neck, chest, abdomen and pelvis with contrast, at an interval that is dictated by the pace of prior disease-progression if known, and typically a period of at least one year. Most patients with refractory advanced disease have an aggressive course and a life expectancy of 3-6 years after the discovery of distant metastases. However, metastatic DTC can be asymptomatically stable for long periods of time, in particular in young patients with small lung metastases from a well differentiated papillary or follicular carcinoma and in such patients the benefits of novel therapies may be largely outweighed by drug toxicities.

Table 1--MANAGEMENT OF REFRACTORY DTC
L-T4 treatment with serum TSH <0.1mU/l
Focal treatments when needed
Imaging follow-up every 4-6 months
STABLE DISEASE- continued active follow-up
PROGRESSION : >20% BY RECIST criteria in 6-12 months and significant tumor burden
INCLUSION IN A TRIAL- --Chemotherapy-low efficacy, significant toxicity (eg-doxorubicin=<5% PR, median PFS= 7 months) --Targeted Therapy as first line (ATA, Cooper, Thyroid 2009, 19 :1167)

TREATMENT OF REFRACTORY THYROID CANCER--INDICATION FOR SYSTEMIC THERAPY
The decision to initiate systemic treatment is based on several parameters, including tumor burden, disease progression, symptoms, or high risk of local complications.
a) *Progression rate can be evaluated by the doubling time of serum Tg (12)*,
b) *Progression should always be confirmed before initiating a treatment with TKI by imaging using Response Evaluation Criteria in Solid Tumor (RECIST)* (13). RECIST consists in measuring the longest diameter of each target lesion (lesion >1cm in diameter) at each

imaging control and in comparing the sum of these diameters: progression is defined by an increase of this sum by 20% or by the appearance of new lesions; partial response is defined by a decrease in this sum by 30% and complete response is the disappearance of all visible lesion.
Patients with multiple lesions >1-2 cm and with progression within less than 12 months are considered for systemic treatment. On the contrary, patients with few and/or small lung lesions <1cm, and those with no evidence of progression are considered for active follow-up (2).
c) *Some patients with large tumor burden and lacking ^{131}I uptake and for whom there is no data on progression, may be considered for systemic treatment based on uptake of FDG on PET scanning or even on primary tumor histology (7,8), but only when active surveillance is not feasible, or there is a high risk of complications.*

CHOICE OF SYSTEMIC THERAPY
In the past, cytotoxic chemotherapy was used in these patients, but response rates obtained with doxorubicin, the most frequently used agent ranged from 0% to 20%, all responses being partial and transient, and toxicity was significant. The combination with cisplatinum did not improve the efficacy but increased the toxicity (14). Experience is limited with other cytotoxic agents, but reported results were not better than with doxrubicin, and for this reason the ATA recommendations stated in 2009 that kinase inhibitors should be used as first line treatment in patients with refractory DTC in whom progression has been documented. However, toxicities of kinase inhibitors are significant and include fatigue, diarrhea, hypertension and skin toxicities. They occurred in the majority of patients and led to dose reduction in 11–73% of patients and to drug withdrawal in 7–25%. This is why patients' education is mandatory and why these treatments should be managed by experienced teams.
Also, tumor responses were observed in only a fraction of patients and most were partial and transient; improvement of progression free survival has been documented in only one phase 2 trials (15) and in one phase 3 trial (16). There is no evidence that treatment at an early stage may be more efficient than a treatment performed at a later stage when progression has been documented. The duration of treatment is not yet validated and, for this reason, treatment is usually given as long as toxicities remain manageable and there is no evidence of tumor progression. This is the rationale for initiating these treatments only in patients with significant tumour burden and with documented progressive disease.

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