



LETTER TO THE EDITOR

Considerations about document of Spanish consensus for the management of patients with advanced radioactive iodine refractory differentiated thyroid cancer (CDT-RAI)[☆]



Consideraciones con relación al documento de consenso español sobre el manejo del cáncer diferenciado de tiroides en fase avanzada y resistente al tratamiento con radioyodo (CDT-RAI)

Dear Editor,

We congratulate the authors of the Spanish consensus on the management of patients with advanced radioactive iodine-refractory differentiated thyroid cancer (RAI-DTC)¹ for their efforts to focus attention on this type of cancer that compromises patient survival and poses so many questions for medical teams. However, we would like to point to some pending issues that may seem confusing in the document, referring mainly to systemic treatments.

Although there is no complete agreement on the definition of iodine refractoriness/non-avidity, we think that the main problem is to ascertain whether this group shows homogeneous behavior. In the Durante et al. study,² on which the DECISION and SELECT^{3,4} studies are based, the independent variables for survival considered included advanced age, male sex, poorly differentiated histology, the extent of the disease, and the presence or absence of initial iodine uptake. The latter is one of the most statistically significant factors, and introduces a “new” factor: the presence or absence of “primary iodine resistance”. However, DECISION and SELECT^{3,4} do not consider the absence of iodine uptake at diagnosis, and one may therefore wonder if the arms

were well balanced with regard to this apparently important variable. In fact, it is unknown whether uptake itself may indicate a more benign behavior of the tumor, rather than a benefit of treatment in patients who take up iodine but do not achieve a complete response (CR) to ¹³¹I.

The document does not specify, although it seems important, when progression should be considered slow or rapid. In the DECISION and SELECT studies, progression in approximately one year was considered rapid. However, in the placebo arms of both studies there was a substantial proportion (one third) of patients with stable disease for more than six months, but we do not know for how much longer. Therefore, where do we draw the line regarding time to progression in asymptomatic patients?

Both studies left many issues unresolved, and there are variables that need to be analyzed. One of the most immediate questions concerns the very different behavior of their control groups, despite theoretically meeting very similar selection criteria and having similar baseline characteristics.

1. In DECISION and SELECT, respectively, 74% and 54% of patients achieved stable disease. In addition, one third of both groups achieved long-term stable disease (longer than 6 months) without active treatment. Thus, patients who achieved stable disease with treatment coexist with those with stable disease without treatment, a fact which has not been analyzed.
2. One-year progression-free survival (PFS) in the placebo group of both studies was over 30% in the DECISION study, and about 10% in the SELECT study, and decreased at two years to slightly over 10% and 5% respectively. These differences may be partially explained by the inclusion of patients receiving second-line treatment in the SELECT study. On the other hand, in the DECISION study some patient subgroups showed some questionable advantages in PFS as compared to the placebo group: male sex, small metastases (<71 mm), and few lesions (<5 lesions), patients receiving more than 600 mCi.
3. As regards survival, it might be expected that lenvatinib, which achieves a high response rate and greatly improves PFS, would change the course of the disease to a greater extent than sorafenib. However, patients treated with lenvatinib have a lower chance of survival at one and two years than patients treated with sorafenib, despite

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having received a subsequent line of treatment more frequently.

The prevalence of some adverse events of this treatment, such as asthenia, anorexia, and weight loss, increases over time, and the prevalence of other controlled events (with medication) is very high.⁵ The quality of life analysis performed in the DECISION study⁶ showed its impairment with treatment. The SELECT study⁴ reported frequent and severe toxicities associated with toxic death, and a quality of life improvement is therefore hardly to be expected (especially in asymptomatic patients, not quantified in this study). We conclude that the results reported in both studies at least raise some doubts regarding the treatment of certain patients.

Finally, chemotherapy has been evaluated infrequently and often inadequately, as studies have included patients with all histological types. Four studies^{7–10} on RAI-DTC alone have been reported, and their results may be as promising as those achieved with other currently tested drugs. A phase II study⁷ where a regimen consisting of carboplatinum-4epiADM and TSH hyperstimulation was administered reported a response rate (RR) of 43% (7% of CR) and a clinical benefit (CB) of 93%. Another study⁸ using a combination of gemcitabine and oxaliplatin reported a RR of 57% (7% CR) and a CB of 86%. It should be noted that two studies^{7,10} assessed response at 10–40 weeks and at 40–49 weeks respectively, which indicates durable responses. Response durations varied between 6 and 12 months,⁹ 15.6 months,⁸ and 22 months,¹⁰ which is hardly short. Only Spano et al.⁸ analyzed PFS, and found a median of 10.1 months (1.6–22 months), which is similar to the value found in the DECISION study.³ In the Spano et al. study,⁸ median survival was not achieved after a 19.8-month follow-up (1.6–62.9 months) with 10 of 14 patients still alive (71%), and an estimated two-year survival rate of 80%. Median survival was not reached either in the Santini et al.⁷ study 21 months (15–34) after treatment start, with 64% of patients still alive at that time. For these reasons, it cannot be stated that *“Several studies have assessed the activity of certain agents with variable results, RRs ranging from 0% to 20%, short-lasting responses, with no complete remissions, and with no impact on overall survival”*. We think that the results may be promising, as are those found with other drugs, but additional research is certainly needed.

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Ana Albero Tamarit^a, Alberto Torres Cuadro^{b,*},
Tomas Martín Hernández^b

^a Unidad de Gestión Clínica de Oncología, Hospital Universitario Virgen Macarena, Sevilla, Spain

^b Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen Macarena, Sevilla, Spain

* Corresponding author.

E-mail address: casablanca37@terra.com
(A. Torres Cuadro).