The placebo effect in thyroid cancer: a meta-analysis

María Llaveró-Valero¹, Francisco Guillén-Grima^{2,3,4}, Carles Zafon⁵ and Juan C Galofré^{1,3}

Departments of ¹Endocrinology and Nutrition and ²Preventive Medicine, Clínica Universidad de Navarra, University of Navarra, Pío XII, 36, 31080, Pamplona, Spain, ³IdiSNA, Navarra's Health Research Institute, Pamplona, Spain, ⁴Department of Health Sciences, Public University of Navarra, Pamplona, Spain and ⁵Department of Endocrinology, Hospital Vall d'Hebron, and Diabetes and Metabolism Research Unit, Vall d'Hebron Institut de Recerca (VHIR), Universitat Autònoma de Barcelona and CIBERDEM (ISCIII), Barcelona, Spain

Correspondence should be addressed to J C Galofré
Email
jcgalfre@unav.es

Abstract

Context: The natural history of advanced thyroid malignancies is largely unknown. The outcome of patients included in the placebo arm of clinical trials could be reflective of their therapy-free evolution.

Objective: To analyze the response rate, symptoms and adverse effects of locally advanced or metastatic differentiated (DTC) and medullary thyroid cancer (MTC) in patients treated with placebo in clinical trials.

Design: PubMed (MEDLINE) and SCOPUS databases were searched through September 2015 to identify high-quality randomized controlled clinical trials. We included studies that recruited patients with DTC or MTC with a placebo arm.

Methods: We conducted a meta-analysis for each category of response rate, adherence to treatment, and adverse events. An empirical Bayesian random-effect model was used.

Results: We identified five clinical trials. DTC and MTC were independently analyzed. In the placebo arm, no complete response was observed; partial response occurred in 1.6% (0.6–3) and 6.4% (3.4–10.3) of DTC and MTC respectively; stable disease was described in 40.5% (34.6–46.9) and 53.9% (44.3–64.4) of DTC and MTC respectively. DTC reached a disease control rate of 42.3% (36.2–48.9) and MTC of 60.2 (50.1–71.4). Treatment discontinuation rate was 3.5% (1.9–5.5) in DTC and 5.7% (3.0–9.4) in MTC. Rate of dose reduction was 7.3% (4.8–10.5) in DTC and 6.2% (3.3–10.0) in MTC.

Conclusions: This meta-analysis provides extensive data on the response rate and adverse effects of locally advanced or metastatic DTC and MTC in patients treated with placebo. These results may be used for comparisons with results from clinical trials without a placebo arm.

European Journal of
Endocrinology
(2016) 174, 465–472

Introduction

The natural history of thyroid cancers is largely unknown simply because hardly any patients go untreated. However, from experience, we recognize that these malignancies (with the exception of anaplastic thyroid cancer) are generally treatable diseases with an indolent course and fair likelihood of complete cure. Nearly all differentiated thyroid cancers (DTC) respond very well to surgery plus radioactive iodine therapy (when necessary). On the other hand, medullary thyroid cancer (MTC), while certainly more aggressive, have a 10-year survival

rate for operated patients with stage I and II is 90–100%. One of the few pieces of data about the spontaneous evolution of untreated micro (diameter <1 cm) DTC comes from a Japanese study (1). Their results convincingly concluded that a substantial proportion (~70%) of papillary microcarcinomas remains stable or even regresses spontaneously. Nonetheless there is extensive experience showing that some patients with aggressive DTC or MTC do not respond to conventional management. Unfortunately, the chance of cure for these patients

with progressive and resistant-to-therapy disease is extremely minimal in those cases.

Since the early days of the present century, a new paradigm in the management of the advanced thyroid cancers has been developed (2). The availability of tyrosine kinase inhibitors (TKI) in the war chest against metastatic thyroid malignancies has improved these patients' outcome. Over the last 15 years, the number of clinical trials testing novel targeted therapies on patients with advanced thyroid malignancies has rapidly increased. However, the common TKI adverse effects and questionable improvement in terms of the quality of life of patients under these therapies have reduced the enthusiasm that was initially elicited by these drugs. Notwithstanding the drawbacks, some of these compounds have gone to phase III clinical trial stage and there are highly active and world-class research groups looking for safer and more effective molecules against thyroid cancer (3).

Employing state-of-the-art methodology in order to fully understand the true efficacy of the tested compounds, some recent clinical trials have included a placebo group for comparing the results with the intervention group. Thus a close examination of the outcome of the placebo-treated patient group may provide invaluable information and permit the tracing of what could be the natural history of locally advanced or metastatic thyroid cancer. Accordingly, we decided to retrieve and analyze all placebo-treated patients with advanced thyroid cancer (either DTC or MTC) from clinical trials that included this type of control arm. Our aim was to gather information (albeit partial) about the spontaneous evolution of the aggressive disease and the presence of 'placebo-related adverse effects.' The information we present here could be useful for making comparisons with the results of ongoing clinical trials with no placebo arm.

Subjects and methods

Search strategy for the identification of studies

PubMed (MEDLINE) and SCOPUS were searched through September 2015 for studies satisfying inclusion criteria. We used the keywords 'Thyroid Cancer,' 'Differentiated Thyroid Cancer,' 'Medullary Thyroid Cancer,' 'Tyrosine Kinase Inhibitors,' 'Adverse Effects,' combined with 'Randomized,' 'Placebo,' 'Clinical Trial,' and 'Randomized Controlled Trial.' No language filters were used. After the selection of articles, we manually searched for potential new papers from the reference lists. Two investigators (M L-V and J C G) evaluated the studies.

Inclusion criteria

Studies were included in the meta-analysis if they met the following criteria. They had to involve: i) patients with locally advanced or metastatic DTC or MTC and ii) randomized controlled clinical trials with a placebo arm. Reviews, letters and commentaries were excluded. Thyroid cancer patients were defined according to what was previously established in the primary studies. We independently analyzed DTC and MTC.

Quality evaluation

The quality score was determined following the Jadad method (4) (Supplementary Table 1, see section on supplementary data given at the end of this article). The score evaluates the quality of selection, sample size and losses to follow-up, and was specifically developed for meta-analysis of clinical trials.

Data extraction

We recorded the following characteristics from each study: i) demographics (number, mean age and sex of the subjects), ii) geographical area where the study was conducted, iii) Eastern Cooperative Oncology Group (ECOG) status, iv) histology of the tumor, v) information about past medical history, vi) response to placebo treatment, vii) adherence to placebo treatment, and viii) number and type of 'placebo-related' adverse events.

Following the criteria of the clinical trials, responses to placebo treatment were classified according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (5). RECIST categories are summarized as follows: i) complete response (CR): the disappearance of all target lesions; any pathological lymph nodes must have reduction in short axis to <10 mm, ii) partial response (PR): a decrease of at least the 30% in the sum of diameters of target lesions taking as reference the baseline sum of diameters, iii) stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increased to qualify for progression disease (PD), iv) PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm, and v) controlled disease (CD) rate was defined by the sum of CR, PR and SD.

The adherence to the placebo treatment was classified as such: i) full adherence, ii) permanent discontinuation of the treatment, iii) temporary interruption of the treatment and iv) reduction of the treatment dosage.

The 'placebo-related' adverse events were divided quantitatively and qualitatively. The frequency and number of adverse effects included: hypertension, nausea, diarrhea, fatigue, asthenia, decreased appetite, weight loss, Palmar-Plantar erythrodysesthesia (hand-foot syndrome or HFS), alopecia, rash and desquamation, and abdominal pain.

Quantitative analysis (meta-analysis)

The meta-analysis was focused on the outcome of those patients treated in the placebo arm of the retrieved clinical trials. The meta-analysis integrated i) the response to treatment, ii) the adherence to treatment and iii) the presence of adverse effects. Separate meta-analyses were conducted on DTC and MTC trials.

Instead of a frequentist or classic statistical approach, we used a Bayesian model because we evaluated a proportion meta-analysis because it deals more adequately with heterogeneity than the classic random model as we explain elsewhere (6). We provide 95% credibility intervals that indicate that the real value is between these intervals with a probability of 95%. The empirical Bayesian random-effects model accommodates heterogeneity by assuming that true frequency differs across studies. Each meta-analysis was performed to provide a global estimation using the confidence profile method employed by Fast*Pro Software (7), which is widely used for Bayesian proportion meta-analysis (6).

It was not possible to perform the meta-analyses neither on all categories of adverse events nor on all categories of responses to treatment due to the insufficiency of data available in the original articles. The trial conducted by Wells *et al.* (8) failed to mention the number of patients randomized to placebo who have PD. For the same reason, we did not carry out the meta-analyses of rate of adverse events, adverse events grade ≥ 3 , and rate of treatment interruption in those patients retrieved from the two MTC clinical trials that eventually were selected (8, 9). In relation to DTC, we did not perform the meta-analyses on the incidence of asthenia because the SELECT study (10), evaluated asthenia and fatigue altogether.

Results

Search results

We identified 86 articles that met the inclusion criteria. Studies were excluded because either the title or the abstract did not satisfy the inclusion criteria (50 papers),

or because they were related to a different type of cancer (nine studies). The remaining 27 studies were clinical trials (phase I, II or III) evaluating the efficacy of TKI in thyroid cancer. After analysis of these trials, we identified five studies with a placebo arm that eventually fulfilled the inclusion criteria of our meta-analysis. Three studies were focused on DTC and are identified in the present article as DTC 1 (11), DTC 2 (12) and DTC 3 (10). The remaining two studies admitted MTC patients and are labeled in this paper as MTC 1 (8) and MTC 2 (9). All but DTC 1 (11) were phase III clinical trials (Fig. 1).

Differentiated thyroid cancer

The entire DTC placebo-treated sample included 414 individuals, consisting of groups of 73 (DTC 1) (11), 210 (DTC 2) (12) and 131 (DTC 3) (10) individuals, in the three different trials. All subjects had evidence of targeted lesions and were assessed following RECIST criteria throughout the observation period of their respective studies. All patients were diagnosed with locally advanced or metastatic 131 iodine refractory DTC.

Figure 1
Flow chart of the meta-analysis.

Clinical Study	M Llaverro-Valero and others	Placebo and thyroid cancer: a meta-analysis	174:4	468
----------------	------------------------------	---	-------	-----

The results and demographic characteristics of the studies are set forth in [Table 1](#).

Response rate ► No CR was observed in any DTC patient included in the placebo arm. PR occurred in 1.6% (95% CI, 0.6–3.0) of the patients included in the intention-to-treat placebo arm while SD was described in 40.5% (95% CI, 34.6–46.9) of them. Therefore the CD rate was 42.3% (95% CI, 36.2–48.9). On the other hand, PD was seen in 63.3% (95% CI, 55.9–71.2) of the patients. Detailed information is compiled in [Tables 2 and 3](#).

Adherence to treatment ► Permanent discontinuation of treatment among the placebo-treated patients was 3.5% (CI 95%, 1.9–5.5). Temporary interruption of the therapy was registered in 22.9% (CI 95%, 18.1–28.3) of the placebo arm subjects, whereas the rate of dose reduction was 7.3% (CI 95%, 4.8–10.5) ([Tables 2 and 3](#)).

Adverse events ► Adverse events attributed to therapy occurred in 76.8% (95% CI, 67.7–86.3) of the subjects with advanced DTC under placebo treatment. The prevalence of severe adverse events (grade 3 or worse) took place in 19.8% (95% CI, 15.7–24.3) of them, although the

frequency in the three DTC studies ranged between 26.3% in DTC 2 ([12](#)) and 9.9% in DTC 3 ([10](#)).

A separate meta-analysis was also conducted on each of the most frequent placebo-related adverse events reported in the clinical trials, and the results are summarized in [Tables 4 and 5](#).

Medullary thyroid cancer

As mentioned, there were two clinical trials that admitted subjects with advanced MTC. The MTC 1 ([8](#)) placebo arm recruited 100 subjects and the MTC 2 ([9](#)) included 111 individuals in the placebo group, giving a total of 211 subjects for the meta-analysis. All of these patients were adults who had unresectable locally advanced or metastatic MTC. The demographic characteristics of the studies are shown in [Table 1](#).

Response rate ► Similar to DTC, there was no CR found among the MTC patients included in the placebo arm. PR and SD occurred in 6.4% (95% CI, 3.4–10.3) and 53.9% (95% CI, 44.3–64.4) of the intention-to-treat placebo individuals respectively. CD rate was 60.2% (95% CI, 50.1–71.4). Nevertheless, it is important to

Table 1 Demographics of the placebo arm from the thyroid cancer studies.

Variable	Subgroups	Differentiated thyroid cancer	Medullary thyroid cancer
<i>n</i>		414	211
Median age (years)		62.6	54.2
Female sex (%)		54	40.3
Region (%)			
	Europe	63.3	–
	North America	18.1	–
	Other countries ^a	18.6	–
ECOG or WHO performance status (%)			
	0–1	–	54
	1–2	–	46
	2 or 3	96.4	–
DTC histology (%)			
	Papillary	50.9	NA
	Follicular	12.8	NA
	Poorly differentiated	15.2	NA
Origin (%)			
	Sporadic or unknown	NA	6.2
	Hereditary	NA	93.8
RET mutation status (%)			
	Positive	NA	51.2
	Negative	NA	7.6
	Unknown		41.2
Previous systemic therapies (%)			59.9
Previous targeted therapies ^b (%)		7.2	
Metastatic disease (%)			
	Lymph nodes		73
	Lungs and pleura	95.9	58.8
	Bone	31.6	45.5
	Liver		62.1
Organs with systemic disease (%)			
	0–1		10.9
	≥2		89.1

NA, not applicable or nonavailable.

^aOther countries include Brazil, Chile, Russia and Asian nations. We assumed all patients included in the vandetanib trial to be European ([11](#)).

^bSorafenib trial ([12](#)). The authors excluded those patients who had received previous targeted therapies.

Clinical Study	M Llaverro-Valero and others	Placebo and thyroid cancer: a meta-analysis	174:4	469
----------------	------------------------------	---	-------	-----

Table 2 Results in the placebo arm of thyroid cancer clinical trials: response rate and adherence to therapy. Data are presented as *n* (%).

	Differentiated thyroid cancer			Medullary thyroid cancer	
	DTC 1	DTC 2	DTC 3	MTC 1	MTC 2
CR	–	–	–	–	–
PR	4 (5.5)	1 (0.5)	2 (1.5)	13 (13)	0 (0)
SD	27 (37)	67 (33.2)	71 (54)	58 (58)	52 (50)
CD	31 (42.5)	68 (33.8)	73 (55.7)	71 (71)	52 (50)
PD	61 (83.6)	150 (71.8)	51 (39.7)	–	35 (33.6)
Discontinuation	4 (6)	8 (3.8)	3 (2.3)	3 (3)	9 (8)
Interruption	11 (15.3)	54 (25.8)	24 (18.3)	–	–
Dose reduction	2 (2.7)	19 (9.1)	6 (4.6)	3 (3)	10 (9)

CR, complete response; PR, partial response; SD, stable disease; CD, controlled disease; PD, progression disease.

point out that 12 out of 13 PR of the MTC 1 trial (8) were observed in the placebo arm in patients who were crossed to the drug arm and received vandetanib in the open-label phase of the study. Detailed information is compiled in Tables 2 and 3.

Adherence to the treatment ► Up to 6.2% (CI 95%, 3.3–10.0) of the placebo treated individuals needed a dose reduction because of adverse events. The rate of discontinuation of the placebo therapy due to adverse events was 5.7% (CI 95%, 3.0–9.4) (Tables 2 and 3).

Adverse events ► Like in DTC, separate meta-analyses were carried out on the most frequent placebo-related adverse events reported in the two selected studies and the results are presented in Tables 4 and 5.

Discussion

TKI have revolutionized the treatment of several cancers. In advanced thyroid cancer, a number of clinical trials tested their effectiveness with encouraging results. More recently, a number of randomized phase III clinical trials with placebo have been published.

Randomized double-blinded trials with a placebo control are considered the gold standard in clinical research. The so-called ‘additive model’ assumed that drug and placebo effects are additive in the drug arm of the study, thus subtracting the response in the placebo arm from the response in the drug arm would allow to researchers to assess the true efficacy of a drug (13). The placebo effect has been defined as ‘the effect seen in a patient who has received an intervention which is believed to lack a specific action’ (14, 15). Since the first modern description by Beecher in 1955 (16), it has been reported that over 35% of patients are improved or cured

by the placebo effect, although it has been suggested that this rate of response is overestimated (14). Greater effects are observed for subjective sensations, psychological disorders or for relief of symptoms. Certainly, psychiatry is the field where placebo effects have been researched the most (17). The exact mechanisms of the placebo effect have not yet been adequately explained and several models have been proposed in an attempt to do so. There is a recent evidence that genetic variations in neurotransmitter pathways can modify placebo effects, opening a new area of research that some authors have called the placeboome (18). Several meta-analyses have been published which purport to establish the power of the placebo effect for specific disorders, including minimally invasive interventions, some with controversial results (19, 20). However, in the field of oncology, available data are scarce. Moreover, to our knowledge, this is the first ever such study in thyroid cancer.

Chvetzoff & Tannock (14) published a systematic review in 2003. They included 36 randomized placebo-controlled oncologic trials, from 1966 to 2000. The vast

Table 3 Meta-analysis of the response rate and adherence to therapy in the placebo arm of thyroid cancer clinical trials. Data are presented as percentage (95% CI).

	Differentiated thyroid cancer	Medullary thyroid cancer
CR	0 (0)	0 (0)
PR	1.6 (0.6–3.0)	6.4 (3.4–10.3)
SD	40.5 (34.6–46.9)	53.9 (44.3–64.4)
CD	42.3 (36.2–48.9)	60.2 (50.1–71.4)
PD	63.3 (55.9–71.2)	–
Discontinuation	3.5 (1.9–5.5)	5.7 (3.0–9.4)
Interruption	22.9 (18.1–28.3)	–
Dose reduction	7.3 (4.8–10.5)	6.2 (3.3–10.0)

CR, complete response; PR, partial response; SD, stable disease; CD, controlled disease; PD, progression disease.

Clinical Study	M Llaverro-Valero and others	Placebo and thyroid cancer: a meta-analysis	174:4	470
----------------	------------------------------	---	-------	-----

Table 4 Most common adverse events in the placebo arm of thyroid cancer clinical trials. Data are presented as *n* (%).

	Differentiated thyroid cancer			Medullary thyroid cancer	
	DTC 1	DTC 2	DTC 3	MTC 1	MTC 2
Hypertension	4 (6)	26 (12.4)	12 (9.2)	5 (5)	5 (4.6)
Nausea	11 (15)	24 (11.5)	18 (13.7)	16 (16)	23 (21.1)
Diarrhea	12 (17)	32 (15.3)	11 (8.4)	26 (26)	36 (33)
Fatigue	13 (18)	53 (25.4)	NA	23 (23)	31 (28.4)
Asthenia	NA	NA	NA	11 (11)	16 (14.7)
PPE/HFS	NA	20 (9.6)	1 (0.8)	NA	NA
Anorexia	10 (14)	10 (4.8)	15 (11.5)	12 (12)	17 (15.6)
Weight loss	NA	29 (13.9)	12 (9.2)	9 (9)	11 (10.1)
Abdominal pain	NA	8 (3.8)	1 (0.8)	5 (5)	7 (6.4)
Rash or desquamation	3 (4)	24 (11.5)	2 (1.5)	11 (11)	11 (10.1)
Alopecia	NA	16 (7.7)	5 (3.8)	NA	NA

PPE/HFS, Palmar–Plantar erythrodysesthesia/hand–foot syndrome; NA, not applicable or nonavailable.

majority of patients included had advanced cancer, metastatic cancer or terminal cancer. Criteria for tumor response were inconsistent and in many cases non-rigorous, but they found a response rate ranging from 2 to 7% in the placebo arm. Authors remarked that positive response was more common for trials of slowly growing tumors and when the duration of response to therapy was shorter. Although having a worse prognosis than in non-refractory well-differentiate thyroid cancer, evolution of advanced DTC or MTC is still more indolent than the majority of epithelial neoplasms. In our study, all trials included the widely used RECIST criteria to evaluate tumor response. With this objective measurement tool, we observed a low percentage of PR in DTC (1.6%) clinical trials in the placebo arm. Moreover up to 40% of patients in DTC studies achieved CD among the placebo-treated group after a follow up of 6 months. PR rose to 6.4% in MTC subjects and CD was present in more than half of these cases.

Some authors differentiate between placebo and nocebo effect according to its positive or negative impact on health expectations. The term placebo applies to a therapeutic encounter that benefits the health status because of the patient's belief in its effectiveness, whereas nocebo applies to an intervention that worsens the health status due to the patient's failure to believe in the healing power of the intervention (17). On the other hand to consider the placebo as an 'inert substance' is erroneous (21). In a broad sense, any circumstances that influence a patient's health care (from a medical team to the hospital environment) influence the therapeutic effect. A positive attitude of healthcare staff always matters and has a substantial impact on treatment outcome, though it is difficult to quantify (22). Empathic and professional health care create a cognitive–affective–sensory orientation, tapping into conscious and subconscious mechanisms

that can predispose a patient towards reduced symptom severity and lessen reactivity to underlying pathophysiology (21). Similarly, psychosocial factors that modulate therapeutic placebo effects also have the potential to cause adverse consequences (21).

TKIs are generally better tolerated than traditional chemotherapy. However, their use is clearly accompanied by several (and sometimes serious) toxic effects. Normally cancer patients are informed of this potential toxicity when they receive the information prior to recruitment for the clinical trial. This knowledge may indeed contribute to the nocebo effect. Although there is no evidence that placebos can shrink tumors, some experiments have shown that common symptoms of cancer and adverse events related to cancer therapies are responsive to placebo treatments (21). In the aforementioned systematic

Table 5 Meta-analysis of the most common adverse events in the placebo arm of thyroid cancer clinical trials. Data are presented as percentage (95% CI).

	Differentiated thyroid cancer	Medullary thyroid cancer
Hypertension	10.1 (7.2–13.4)	4.8 (2.3–8.2)
Nausea	12.7 (9.5–16.4)	18.8 (13.3–25.1)
Diarrhea	13.2 (10–17)	29.8 (22.9–37.7)
Fatigue	23.5 (18.2–29.5)	26 (19.5–33.3)
Asthenia	NA	13.0 (8.6–18.3)
PPE/HFS	6.2 (3.8–9.1)	NA
Anorexia	8.4 (5.8–11.4)	13.9 (9.3–19.5)
Weight loss	12.1 (8.7–16)	9.6 (5.9–14.3)
Abdominal pain	2.6 (1.6–4.6)	5.8 (3.0–9.5)
Rash or desquamation	6.9 (4.6–9.7)	10.6 (6.6–15.4)
Alopecia	6.2 (3.8–9.1)	NA

PPE/HFS, Palmar–Plantar erythrodysesthesia/hand–foot syndrome; NA, not applicable or nonavailable.

review, Chvetzoff & Tannock (14) found an association in the type and incidence of side effects between the treatment and the placebo arm. Research reviews have estimated that 4–26% of patients who are randomly assigned to placebos in trials discontinue their use because of perceived side effects (21). Although the majority of adverse events were moderate to low in the placebo arms, some trials associated grade-3 toxicity to the placebo, which was a reason for withdrawal patients from the study. In our meta-analysis we found a rate of 76.8% of the subjects with advanced DTC, with a percentage of grade 3 or worse in over 20% of them. However, the rate of discontinuation was only 3.5%. Notably, hypertension, fatigue and gastrointestinal events were the most common complaints, as was found in the drug arm of the trials, as if the placebo was mimicking the TKI. Thus, the side-effect profile of the placebo groups seems to partially reflect the anticipated side effects of the drug (23).

This meta-analysis incorporates all available publications on patients with thyroid cancer who have been treated with placebo through September 2015. Although the number of studies is limited, the information provided is highly relevant. It is possible to perform meta-analysis using as few as two sources of data (24). Undoubtedly, meta-analysis on this topic could and should be conducted in the future as more information comes available. However, based on the reliability of our investigation, we anticipate that the results of future meta-analysis using a greater number of clinical trials will not differ significantly from those presented here, with the only difference being that the future study would likely narrow the CIs.

In summary, in this meta-analysis, we have found a low response rate among the placebo-treated patients with advanced or metastatic DTC or MTC. However, a significant percentage of those patients achieve substantial CD. On the other hand, we have found that placebo and nocebo effects in advanced DTC and MTC randomized clinical trials were similar to those published in the field of oncology. The slowly growing tumor profile and the short follow-up registered in all the studies analyzed must be taken into account to fully comprehend the real effect of the TKIs.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-1119>.

Declaration of interest

M Llaverro-Valero, F Guillén-Grima, and C Zafon have nothing to disclose. J C Galofré has been a consultant for AstraZeneca, Bayer Healthcare and Genzyme, and has received speaker honoraria from Genzyme and Merck.

Funding

No funding body had any role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

References

- Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, Yokozawa T, Matsuzuka F, Kuma S, Kuma K *et al.* An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid* 2003 **13** 381–387. (doi:10.1089/10507250321669875)
- Galofré JC, Gómez-Sáez JM, Álvarez-Escola C, Álvarez-García E, Anda-Apiñaniz E, Calleja A, Donnay S, Lucas-Martin A, Menéndez Torre E, Navarro González E *et al.* Toma de posición del Grupo de Trabajo de Cáncer de Tiroides de la Sociedad Española de Endocrinología y Nutrición. Use of new molecules in the treatment of advanced thyroid cancer. *Endocrinología y Nutrición* 2011 **58** 381–386. (doi:10.1016/j.endonu.2011.07.001)
- Haugen BR & Sherman SI. Evolving approaches to patients with advanced differentiated thyroid cancer. *Endocrine Review* 2013 **34** 439–455. (doi:10.1210/er.2012-1038)
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ & McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996 **17** 1–12. (doi:10.1016/0197-2456(95)00134-4)
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of National Cancer Institute* 2000 **92** 205–216. (doi:10.1093/jnci/92.3.205)
- Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F & Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 923–931. (doi:10.1210/jc.2013-2409)
- Eddy DM & Hasselblad V. Fast*Pro. Software for metaanalysis by the confidence profile method. San Diego: Academic Press; 1992.
- Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *Journal of Clinical Oncology* 2012 **30** 134–141. (doi:10.1200/JCO.2011.35.5040)
- Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC *et al.* Cabozantinib in progressive medullary thyroid cancer. *Journal of Clinical Oncology* 2013 **31** 3639–3646. (doi:10.1200/JCO.2012.48.4659)
- Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *New England Journal of Medicine* 2015 **372** 621–630. (doi:10.1056/NEJMoa1406470)
- Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gómez JM, Bonichon F, Leenhardt L, Soufflet C *et al.* Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncology* 2012 **13** 897–905. (doi:10.1016/S1470-2045(12)70335-2)
- Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK *et al.* DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014 **384** 319–328. (doi:10.1016/S0140-6736(14)60421-9)

Clinical Study	M Llaverro-Valero and others	Placebo and thyroid cancer: a meta-analysis	174:4	472
----------------	------------------------------	---	-------	-----

- 13 Enck P, Klosterhalfen S, Weimer K, Horing B & Zipfel S. The placebo response in clinical trials: more questions than answers. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 2011 **366** 1889–1895. (doi:10.1098/rstb.2010.0384)
- 14 Chvetzoff G & Tannock IF. Placebo effects in oncology. *Journal of National Cancer Institute* 2003 **95** 19–29. (doi:10.1093/jnci/95.1.19)
- 15 Kaptchuk TJ. Powerful placebo: the dark side of the randomised controlled trial. *Lancet* 1998 **35** 1722–1725. (doi:10.1016/S0140-6736(97)10111-8)
- 16 Beecher HK. The powerful placebo. *Journal of the American Medical Association* 1955 **159** 1602–1606. (doi:10.1001/jama.1955.02960340022006)
- 17 Požgain I, Požgain Z & Degmečić D. Placebo and nocebo effect: a mini-review. *Psychiatria Danubina* 2014 **26** 100–107.
- 18 Hall KT, Loscalzo J & Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends in Molecular Medicine* 2015 **21** 285–294. (doi:10.1016/j.molmed.2015.02.009)
- 19 Fässler M, Meissner K, Kleijnen J, Hróbjartsson A & Linde K. A systematic review found no consistent difference in effect between more and less intensive placebo interventions. *Journal of Clinical Epidemiology* 2015 **68** 442–451. (doi:10.1016/j.jclinepi.2014.11.018)
- 20 Holtedahl R, Brox JI & Tjomsland O. Placebo effects in trials evaluating 12 selected minimally invasive interventions: a systematic review and meta-analysis. *BMJ Open* 2015 **5** e007331. (doi:10.1136/bmjopen-2014-007331)
- 21 Kaptchuk TJ & Miller FG. Placebo effects in medicine. *New England Journal of Medicine* 2015 **373** 8–9. (doi:10.1056/NEJMp1504023)
- 22 Chochinov HM. Dignity and the essence of medicine: the A, B, C, and D of dignity conserving care. *BMJ* 2007 **225** 184–187. (doi:10.1136/bmj.39244.650926.47)
- 23 Enck P & Klosterhalfen S. The placebo response in clinical trials-the current state of play. *Complementary Therapies in Medicine* 2013 **21** 98–101. (doi:10.1016/j.ctim.2012.12.010)
- 24 Valentine JC, Pigott TD & Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis *Journal of Educational and Behavioral Statistics* 2010 **35** 215–247. (doi:10.3102/1076998609346961)

Received 13 November 2015

Revised version received 6 January 2016

Accepted 12 January 2016