

Effectiveness of chemotherapy in advanced differentiated thyroid cancer: a systematic review

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Abstract

In differentiated thyroid carcinoma refractory to radioactive iodine (CDT-RTI), chemotherapy has been considered for decades to be the only systemic therapy with palliative purpose. Phase II studies assessing the efficacy of different chemotherapy outlines have been published. Nevertheless, phase III studies in these tumours have not been performed. Our objective is to evaluate the effectiveness of chemotherapy in patients with CDT-RTI by a systematic review of published studies. Systematic research of the literature in Medline and Embase databases (among others) was carried out. The full texts of selected references were analysed by two independent reviewers and then assessed for risk of bias in each study. We also extracted data using specifically designed questionnaires. Later, a qualitative synthesis of results was performed and pooled data were calculated. We found that 16 studies with 473 patients published in the last 40 years were included out of 509 identified references in databases. Thirteen studies (176 patients) included data on response to treatment and histology. Four studies included 70 patients only with well-differentiated non-medullary tumours. Response rate (RR) was 22.1% (0–57%) for 13 studies, 25% for the 176 patients and 27.1% for the 70 patients, with 2.5, 3.4 and 2.8% complete responses respectively. Survival times could not be assessed or pooled due to the lack of data and heterogeneity of the studies, and was determined to have a high risk of bias. Although it has not been possible to find solid evidence about the efficacy of chemotherapy, the results shown indicate that it may have some effectiveness, although this should be proven with well-designed studies using modern drugs.

Key Words

- ▶ advanced thyroid cancer
- ▶ overall survival
- ▶ chemotherapy
- ▶ adriamycin
- ▶ radioactive iodine refractory thyroid cancer

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Introduction

Differentiated carcinoma accounts for 95% of all the cases of thyroid cancer (Cooper *et al.* 2009). These tumours grow from aberrant follicular cells and are classified histologically as papillary, follicular (including Hürtle's cells carcinoma) or poorly differentiated. Generally, they are

treated effectively with surgery, radioactive iodine (RTI) and suppressive therapy with L-thyroxine. Nevertheless, 7–23% of patients will develop metastases, two-thirds of whom will become resistant to radioactive iodine treatment (Durante *et al.* 2006). In these patients, the median

survival at 10 years can be as low as 25–42%, especially when bone metastases are present (Durante *et al.* 2006, Pacini *et al.* 2006, Cooper *et al.* 2009). Differentiated thyroid carcinoma refractory to radiodine (CDT-RTI) is not considered to be responsive to chemotherapy generally, although for decades this has been considered to be the only systemic treatment with a palliative purpose. Several cytostatics have been tested in small studies with different results, but of all of them adriamycin in monotherapy has been traditionally considered the standard therapy (Gottlieb *et al.* 1972, Leeper & Shimaoka 1980, Poster *et al.* 1981, Schlumberger 1999, Sherman 2010).

In the last decade, the use of new agents has been proposed, which have demonstrated to be relatively useful in different grades of this kind of cancer (Cohen *et al.* 2008, Sherman *et al.* 2008, 2011, Schlumberger *et al.* 2009, Bible *et al.* 2010, Carr *et al.* 2010, Cabanillas *et al.* 2012, National Comprehensive Cancer Network 2013), although multiple side effects of their use have been described (hypertension, bleeding, feet-hand syndrome, intense asthenia, weight loss, anaemia) (Illouz *et al.* 2014). Among all of them, sorafenib has been approved by the European Medicines Agency (EMA) and lenvatinib will possibly be validated in due course. Both have been approved by the Food and Drug Administration (FDA) for CDT-RTI (Brose *et al.* 2014, Schlumberger *et al.* 2015), due to the fact that they achieve significantly higher stabilization of the disease and progression-free survival (PFS), although this has only been compared with placebo. Nonetheless, neither of them has displayed evidence of a beneficial effect on survival, probably due to the cross-over allowed in these studies. Also, often side effects of the long-term treatment result in a deterioration of the quality of life of these patients (which is not too damaged initially). Therefore, a thorough assessment of the efficacy and iatrogenic effects of sorafenib and lenvatinib is necessary to preserve the clinical benefit of these therapies.

The objective of this work is to perform a systematic review of the published studies of the effectiveness of chemotherapy, with special emphasis on analysing response rates and overall survival (OS) of patients with well differentiated and non-medullary thyroid tumours, in an advanced stage and resistant to radioactive iodine treatment, symptomatic or on progression of the disease, treated with diverse chemotherapy schemes.

Methodology

A systematic search of the literature using structured search strategies, according to population format,

intervention, comparison and results-outcomes (PICO) was carried out in order to identify the main relevant studies related to the effectiveness of chemotherapy as palliative treatment for well differentiated non-medullary thyroid cancer. Searches were performed from the opening of databases until 1 June, 2014. The development of search strategies was specific for each of the consulted databases: Medline (including PRE-MEDLINE by PUBMED and PUBMED Health), SCOPUS, EMBASE (Evidence Based Medicine) and the Cochrane Library. For the searches in other databases, such as the Centre for Reviews and Dissemination (CRD that includes the databases of DARE, HTA and NHS EED), Emergency Care Research Institute (ECRI) and metasearchers of SCOPUS, open strategies were used using free text. Websites of scientific societies such as the American Thyroid Association (ATA) were also consulted. Additionally, reference lists of the final selection of articles were checked manually to identify other relevant papers. The search was not limited with respect to language or type of study and it was carried out from 1974 onwards, because from the publication of the work of Gottlieb & Hill (1974), adriamycin was considered the standard chemotherapy regimen. Abstracts for which we could not locate a full-text article were excluded, as were publications in a language other than English, French or German. Disagreements were resolved by consensus.

Titles and abstracts of all retrieved articles were scanned for inclusion by two reviewers with reference to a third reviewer when there was any doubt about their eligibility. When information given in title/abstracts indicated that the study: i) included patients with thyroid carcinoma and ii) included patients subjected to palliative chemotherapy, then the article was considered for the further examination. Furthermore, if there was doubt regarding inclusion on the basis of the title and abstract, the full article was obtained for clarification. Two independent reviewers applied stringent inclusion/exclusion criteria to full papers in order to obtain the final set of included studies.

In this way, studies (prospective and retrospective) with adult patients with diagnosis of locally advanced and non-operable, metastatic well-differentiated non-medullary thyroid carcinoma were included. Both comparative and non-comparative studies were included as were studies that analysed populations with disease in progression and treatment-resistant to radioactive iodine, particularly those that underwent palliative chemotherapy with any drug and/or drug association. Studies with 10 or fewer patients were excluded as series of cases

with a small number of patients could show a high rate of adverse events associated with little experience of this kind of treatment. Letters to the editor, unpublished data or congress abstracts were also excluded.

Data extraction was performed using predefined data extraction forms after a detailed reading of the included full text articles, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A critical reading was made, assessing the methodology proposed using the evaluation tool, Quality Assessment Tool for Case Series Studies proposed by the National Institutes of Health (NIH) specifically for a series of cases (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series.htm) and the tool proposed by the Cochrane

Collaboration for clinical trials. In addition, a qualitative synthesis was made and pooled data (for outcomes of response rate or clinical benefit) was calculated over the total of patients by an analysis of the intention to treat and the gathering of results according to the chemotherapeutic scheme used. The survival probability was calculated with the Kaplan-Meier method when the study did not specify current survival data, but it did specify individual survival data and patient condition at the end of the follow up.

Results

As a result of the described search, 509 references were obtained that were potentially relevant and that assessed

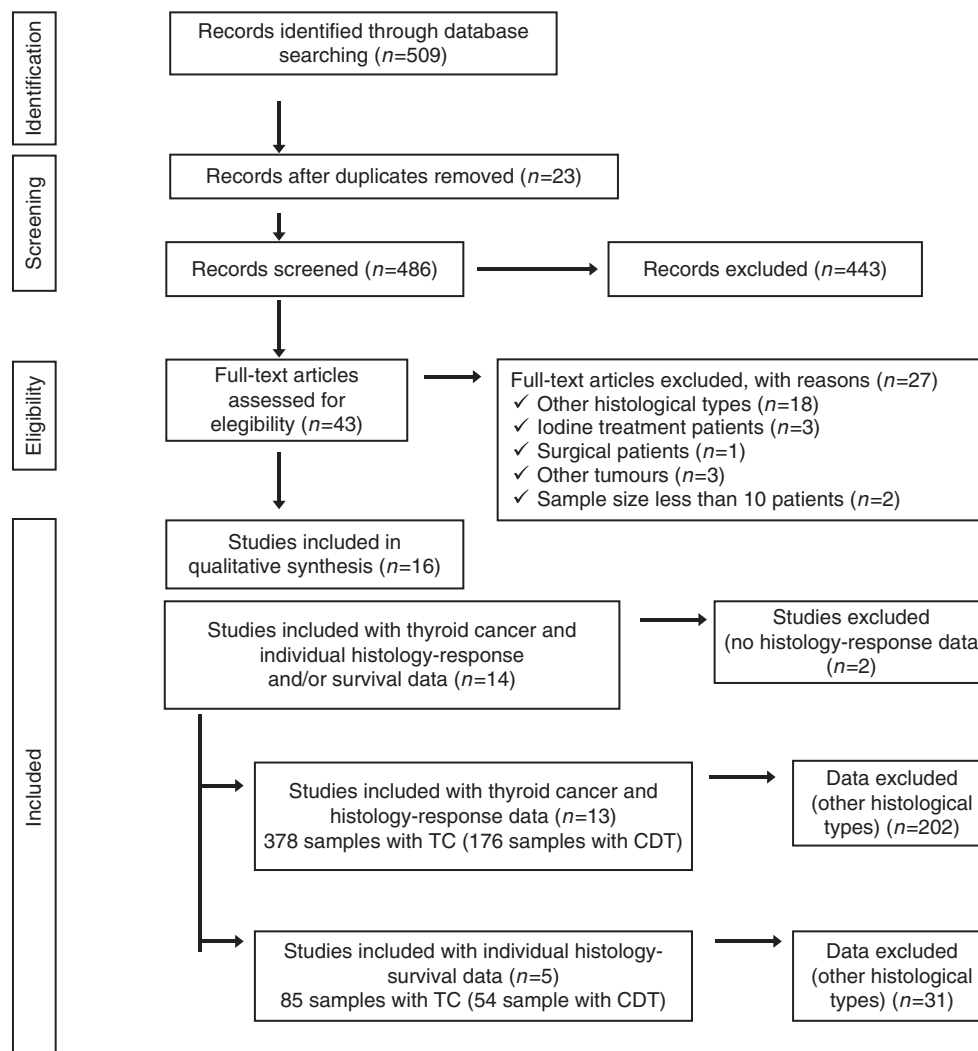


Figure 1

Flow chart of article flow through the systematic review.

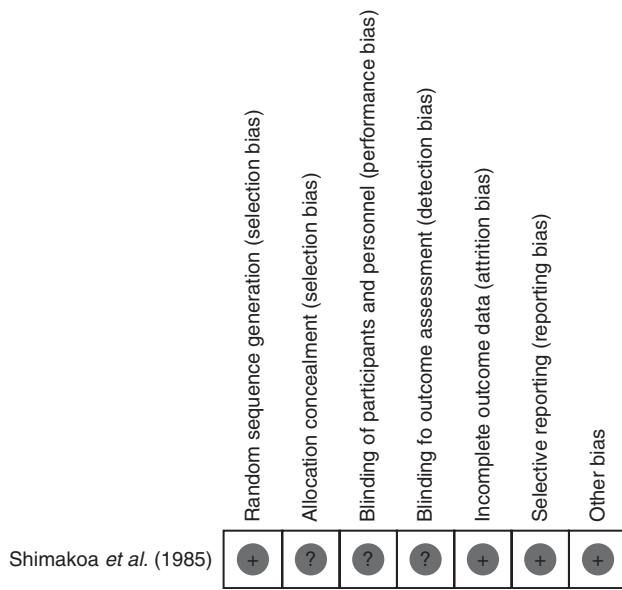
the effectiveness of different chemotherapeutic schemes as palliative treatment for patients with well-differentiated, non-medullary thyroid carcinoma. As displayed in Fig. 1, out of all the references, finally, 16 publications were included in this review (one of which included five series of patients). One was a randomized clinical trial (RCT) (Shimaoka et al. 1985), 13 were phase II studies/prospective series of cases (SC) (Gottlieb & Hill 1974, Benker et al. 1977, Benker & Reinwein 1983, Bukowski et al. 1983, Williams et al. 1986, Hoskin & Harmer 1987, Schlumberger & Parmentier 1989, Droz et al. 1990, Scherübl et al. 1990, De Besi et al. 1991, Santini et al. 2002, Argiris et al. 2008, Spano et al. 2012) and two were on retrospective SC (Matuszczyk et al. 2008, Hussein et al. 2013).

The clinical trial included was published in 1985, whereas the publication period of the series of cases ranged between 1974 and 2013. Three studies analysed the results of the treatment with adriamycin or cisplatin in monotherapy (Gottlieb & Hill 1974, Droz et al. 1990, Matuszczyk et al. 2008), six analysed combinations of adriamycin with cisplatin \pm other drugs ($n=181$) (Shimaoka et al. 1985, Williams et al. 1986, Droz et al. 1990, Scherübl et al. 1990, De Besi et al. 1991, Hussein et al. 2013), five studies the combinations of adriamycin which did not include cisplatin ($n=113$) (Benker et al. 1977, Benker & Reinwein 1983, Bukowski et al. 1983, Droz et al. 1990, Argiris et al. 2008) and another five studies analysed the results of other treatment schemes ($n=86$).

Table 1 Characteristics of studies included in the analysis

Study	Type of study	Treatment scheme	n	Treatment scheme			Median number of cycles (rank)	Mean number of cycles
				First (%)	Second (%)	Third (%)		
Monotherapy with ADM or CDDP								
Gottlieb & Hill (1974)	SC	ADM	30	80	20	0	Responders 9 (4–12)	NS
							Non-responders 2 (1–9)	
Droz et al. (1990) (Study B)	SC	ADM	22	77.2	22.7	0	NS	NS
Droz et al. (1990) (Study C)	SC	CDDP	19	26	63.1	10.5	NS	NS
Matuszczyk et al. (2008)	SC	ADM	22	100	0	0	NS	NS
ADM+CDDP combinations								
Shimaoka et al. (1985)	RCT	ADM vs ADM+CDDP	84	92.9	7.1	0	NS	NS
Williams et al. (1986)	SC	ADM+CDDP+VDS	28	100	0	0	NS	NS
Droz et al. (1990) (Study E)	SC	ADM+CDDP	7	85.7	14.2	0	NS	NS
Scherübl et al. (1990)	SC	ADM+CDDP+VDS	20	85	15	0	NS	NS
De Besi et al. (1991)	SC	ADM+CDDP+BLM	22	100	0	0	NS	NS
Hussein et al. (2013)	SC	ADM+CDDP/CLF+ADM+CDDP	20	100	0	0	NS	4 (2–20)
ADM combinations without CDDP								
Benker et al. (1977)	SC	ADM+BLM+dactinomycin maintenance	21	100	0	0	NS	NS
Benker & Reinwein (1983)	SC	ADM+BLM/ADM	52	100	0	0	NS	NS
Bukowski et al. (1983)	SC	ADM+VCR+BLM+MLF	11	100	0	0	3	NS (1–18)
Droz et al. (1990) (Study A)	SC	ADM+VP+5FU+CLF	12	100	0	0	NS	NS
Argiris et al. (2008)	SC	ADM+IF	17	100	0	0	6	NS (1–13)
Other treatments								
Hoskin & Harmer (1987)	SC	Sequential monotherapy:	29				5	6 (5–7)
		Etoposide (VP16)		100	3.4	6.8		
		Carboplatin		65.5	31	–		
		CDDP		100	13,710.3	10.3		
		ABC		17.2	3.4	10.3		
		Methotrexate		17.2		3.4		
Schlumberger & Parmentier (1989)	SC	Mitoxantrone	17	100	0	0	6	5 (1–12)
Droz et al. (1990) (Study D)	SC	Eliptinium acetate	12	83.3	8.3	8.3	NS	NS
Santini et al. (2002)	SC	Carboplatin +4epiADM	14	85.7	14.2	0	6	5 (1–6)
Spano et al. (2012)	SC	GEMOX	14	100	0	0	9.5	NS (2–17)

RCT, randomized clinical trial, SC, descriptive series; ADM, adriamycin; CDDP, cisplatin; BLM, bleomycin; VDS, vindesine; IF, interferon alpha; VCR, vincristine; MLF, melphalan; VP, VP-16; 5FU, 5-fluorouracil; CLF, cyclophosphamide; GEMOX, gemcitabine+oxaliplatin; ABC, adriamycin+vincristine+bleomycin; NS, not specified.

**Figure 2**

Summary of risks of bias in the clinical trials.

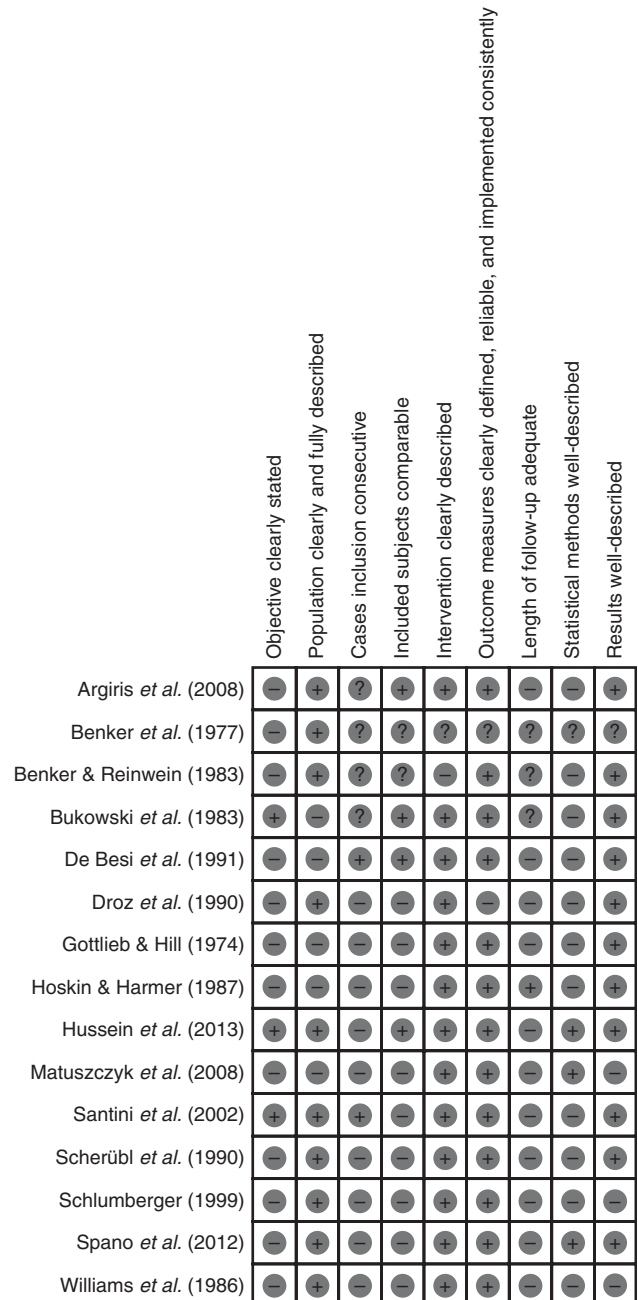
(Hoskin & Harmer 1987, Schlumberger & Parmentier 1989, Droz *et al.* 1990, Santini *et al.* 2002, Spano *et al.* 2012). The majority of patients received the treatment as first line therapy (96.5% between 17 and 100%), with an average of five cycles received (1–20) as shown in Table 1.

The risk of bias in the RCT (Shimaoka *et al.* 1985) was high in relation to the absence of blinding (not only of patients and professionals but also of investigating staff) and the allocation concealment (Fig. 2). For the study of series of cases, the main identified risks of biases were selection and information biases, as a consequence of the investigation's objective lacking a clear description, the inconsecutive inclusion of patients to the study or the absence of comparability between them. The median of follow up was only valuable in one of them, Hoskin & Harmer (1987), because the rest of the studies did not give precise information on that subject or we did not consider it to be adequate (Fig. 3).

Characteristics of the populations included in the studies

Characteristics of the control populations analysed in the included studies are displayed in Table 2. All patients had a confirmed diagnosis of thyroid cancer, with different histology and different differentiation grades (51% were well-differentiated non-medullary carcinomas), in meta-static state and resistant to radioactive iodine treatment. One study provided information about the time lapse

between the initial diagnosis of the disease and the first chemotherapy treatment, which was 26 months (2–240 months) (Droz *et al.* 1990). Another study estimated the time between the initial diagnosis of the disease and the metastatic disease as 9.8 years (1–18 years) (Hussein *et al.* 2013), and the time between the diagnosis of the metastatic disease and the beginning of the chemotherapy as 21.5 months (12–216 months). Seven studies did not

**Figure 3**

Summary of risks of bias in the included case series.

Table 2 Features of the reference population analysed. The studies of Williams *et al.* (1986) and Scherübl *et al.* (1990) only describe the histology of evaluable patients. The studies of Droz *et al.* (1990) and Schlumberger & Parmentier (1989) do not describe the histological subtype (papillary/follicular)

Study	RCT	Monotherapy with ADM ó CDDP	Combinations ADM+CDDP	Combinations ADM without CDDP	Others treatments	Total
Patients included	84	93	97	113	86	473
Evaluable patients	82	87	88	103	84	444
Mean Age (years) (rank)	60 (31–87)	51.5 (14–76)	57 (22–87)	60 (32–89)	56 (19–84)	56.9 (14–89) ^a
Sex (Male/Female), <i>n</i>	35/49	43/47	42/47	21/40	45/41	186/224 ^b
Differentiated histology, <i>n</i>	35	48	47	57	55	242 (51% of total)
Papillary histology, <i>n</i>	NS	9	21	15	24	69
Follicular histology, <i>n</i>	NS	18	19	31	14	83
Hürthle histology, <i>n</i>	NS	5	1	3	2	11
Mixed histology, <i>n</i>	NS	NS	2	0	0	7
Medullar histology, <i>n</i>	10	35	28	17	20	110 (23% of total)
Anaplastic histology, <i>n</i>	39	9	12	38	11	109 (23% of total)
Unknown histology, <i>n</i>	0	1	2	1	0	4 (0.8% of total)
PS0-PS1/Karnowski 80–100	NS	28	39	36	20	123 (63%)
PS2-PS3/Karnowski 40–70	NS	13	27	10	23	73 (37%)

RCT, randomized clinical trial; ADM, Adriamycin; CDDP, cisplatin; PS, performance status; NS, not specified.

^aData for global series from Droz *et al.* (1990) (52 patients).

^bThe studies of Williams *et al.* (1986), Scherübl *et al.* (1990) and Matuszczyk *et al.* (2008) gave information about evaluable patients (410 of 473 patients).

provide data about performance status (PS) of the patients (Gottlieb & Hill 1974, Benker *et al.* 1977, Benker & Reinwein 1983, Bukowski *et al.* 1983, Santini *et al.* 2002, Matuszczyk *et al.* 2008, Hoskin & Harmer 1987). Six studies measured the initial PS using the Eastern Cooperative Oncology Group (ECOG) system (Shimaoka *et al.* 1985, Schlumberger & Parmentier 1989, Droz *et al.* 1990, Argiris *et al.* 2008, Spano *et al.* 2012, Hussein *et al.* 2013) and three using the Karnowski system (Williams *et al.* 1986, Scherübl *et al.* 1990, De Besi *et al.* 1991). In six studies, the inclusion in the study with PS 0-3/Karnowski 40–100 was allowed, with nearly 40% of patients with PS ≥ 2

(Shimaoka *et al.* 1985, Williams *et al.* 1986, Schlumberger & Parmentier 1989, Droz *et al.* 1990, Spano *et al.* 2012, Hussein *et al.* 2013).

Response to treatment and clinical benefit

Classification systems and techniques used for the response assessment in the diverse studies are described in Table 3 (Miller *et al.* 1981, Young *et al.* 1999, Eisenhauer *et al.* 2009). The first response assessment was made after 8–9 weeks in five studies (Gottlieb & Hill 1974, Droz *et al.* 1990, Scherübl *et al.* 1990, Spano *et al.* 2012,

Table 3 Systems of classification and evaluation of response methods

Rating system response	References
OMS	Gottlieb & Hill (1974), Benker <i>et al.</i> (1977), Benker & Reinwein (1983), Bukowski <i>et al.</i> (1983), Shimaoka <i>et al.</i> (1985), Williams <i>et al.</i> (1986), Hoskin & Harmer (1987), Schlumberger & Parmentier (1989), Scherübl <i>et al.</i> (1990), Droz <i>et al.</i> (1990), De Besi <i>et al.</i> (1991), Santini <i>et al.</i> (2002), Argiris <i>et al.</i> (2008)
RECIST	Spano <i>et al.</i> (2012)
EORTC-99	Matuszczyk <i>et al.</i> (2008)
NE	Hussein <i>et al.</i> (2013)
Valuation technique response	
Chest x-ray + bone scan	Gottlieb & Hill (1974), Bukowski <i>et al.</i> (1983), Shimaoka <i>et al.</i> (1985), Schlumberger & Parmentier (1989)
Furthermore, echography	Hoskin & Harmer (1987), Droz <i>et al.</i> (1990), De Besi <i>et al.</i> (1991)
CT	Santini <i>et al.</i> (2002), Argiris <i>et al.</i> (2008), Spano <i>et al.</i> (2012), Hussein <i>et al.</i> (2013)
MRI	Argiris <i>et al.</i> (2008)
PET	Matuszczyk <i>et al.</i> (2008)

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; NE, not specified.

Hussein *et al.* 2013), in three assessment was performed at between 3 and 4 weeks (Bukowski *et al.* 1983, Shimaoka *et al.* 1985, Hoskin & Harmer 1987) and it was performed much later (among 12 and 49 months) in another three studies (Santini *et al.* 2002, Argiris *et al.* 2008, Matuszczyk *et al.* 2008). Five studies did not report this data (Benker *et al.* 1977, Benker & Reinwein 1983, Williams *et al.* 1986, Schlumberger & Parmentier 1989, De Besi *et al.* 1991). Four included information about the time to response in 3 months (three studies) and 9 months (Gottlieb & Hill 1974, Bukowski *et al.* 1983, Droz *et al.* 1990, De Besi *et al.* 1991). The rest of the studies did not provide information on that variable. Considering the studies globally, the RR was 22.2% (0–57%), with 20% PR and 2.5% CR, with an estimate of 27.1% (2.8% CR) in the four studies which just included patients with advanced CDT-RTI (Tables 4 and 5) (Santini *et al.* 2002, Matuszczyk *et al.* 2008, Spano *et al.* 2012, Hussein *et al.* 2013). It was possible to obtain data for assessed histology and response for 13 studies with a total of 179 cases. The RR was 25%, with 3.4% of CR. Eight studies reported detailed response data by histologic subtype (97 patients) (Benker *et al.* 1977, Benker & Reinwein 1983, Bukowski *et al.* 1983, Scherübl *et al.* 1990, De Besi *et al.* 1991, Santini *et al.* 2002, Matuszczyk *et al.* 2008, Spano *et al.* 2012). In 39 cases, there were papillary tumours (RR 25.6%, CR 2.5%). There were 58 patients with follicular tumours (RR 32.75%, CR 5.1%) as shown in Tables 6 and 7.

The clinical benefit (CB) for the global results of studies (405 patients) was 54.3% (25–93%) and in the

studies which were limited to patients with DTC-RTI, 61.4% (Tables 5 and 7). In 129 patients with DTC-RTI (for which individual data were available), the CB was 64.34%, 81.1% and 65.45% in total, papillary and follicular groups respectively (Tables 8 and 9) The mean length of response varied between 3 and 14 months, showing long-lasting CR (60+ months). Seven out of 16 studies estimated the median duration (Gottlieb & Hill 1974, Shimaoka *et al.* 1985, Williams *et al.* 1986, Droz *et al.* 1990, De Besi *et al.* 1991, Spano *et al.* 2012, Hussein *et al.* 2013) with estimates ranging between 3 (Droz *et al.* 1990) and 15.6 months (Spano *et al.* 2012). In three studies, the data about the duration of the response to the chemotherapeutic treatments were stratified based on its quality, noting the long duration of the CR in these studies (between 2.3 and 41.3 months, 30.2+/60+ months) (Bukowski *et al.* 1983, Shimaoka *et al.* 1985, Argiris *et al.* 2008).

PFS and global survival

Three studies analysed the PFS reporting times of 6 months (3–12), 10 months (1.6–22) and 6 months (4.9–7) respectively (Argiris *et al.* 2008, Spano *et al.* 2012, Hussein *et al.* 2013). One study, Argiris *et al.* (2008) expressed the survival as the probability, whereas the rest of the included studies expressed it statistically, this complicated comparisons between data. Five studies collected individual survival data and patients status, and from these survival probability could be calculated (Bukowski *et al.* 1983, Hoskin & Harmer 1987, Schlumberger & Parmentier 1989,

Table 4 Response rate to chemotherapy according to the therapeutic scheme

Study	n	NA (n) %	CR (n) %	PR (n) %	CR+PR (n) RR
RCT	84	2 2.3%	5 5.9%	13 15.4%	18 21%
Monotherapy ADM or cisplatin	93	6 6.4% (0–13.6%)	0 0%	14 15% (0–37%)	14 15% (0–37%)
ADM+ cisplatin	97	7 7.2% (0–21.4%)	2 2% (0–9.5%)	14 14.4% (0–33%)	16 16.4% (0–42.8%)
ADM without cisplatin	113	10 8.8% (0–14.2%)	3 2.6% (0–9.5%)	25 22.1% (0–30.7%)	28 24.7% (0–36.3%)
Others	86	2 2.3% (0–2.3%)	2 2.3% (0–7%)	27 31.3% (0–50%)	29 33.7% (6–57%)
Total	473	27 5.7% (0–21.4%)	12 2.5% (0–9.5%)	93 19.6% (0–50%)	105 22.19% (0–57%)

NA, not assessable; CR, complete response; PR, partial response; RR, response rate=CR + PR/total number of patients; RCT, randomized clinical trial; ADM, adriamycin; rank of outcomes in individual studies of each group.

Table 5 Studies that include only DTC-RTI

Study, year	Santini et al. (2002)	Matuszczyk et al. (2008)	Spano et al. (2012)	Hussein et al. (2013)	Total
Patients characteristics					
Total number of patients	14	22	14	20	70
Number of evaluable patients	14	19	14	20	67
Mean age, years (rank)	57 (39–64)	61 (22–77)	63 (median) (31–85)	65 (54–80)	61.5 (22–85%)
Sex (male/female) <i>n</i> (%)	7/7 (50/50)	8/11 (35/50)	8/6 (57–43)	8/12 (40/60)	31/36 (46.3/53.7%)
Differentiated histology, <i>n</i> (%)	14 (100%)	22 (100%)	14 (100%)	20 (100%)	70 (100%)
Papillary histology, <i>n</i> (%)	6 (21.4%)	7 (32%)	8 (57%)	15 (75%)	36 (51.4%)
Follicular histology, <i>n</i> (%)	6 (21.4%)	15 (68%)	6 (43%)	5 (25%)	32 (45.7%)
Hürtle histology, <i>n</i> (%)	2 (14.2%)	0 (0%)	0 (0%)	0 (0%)	2 (2.8%)
Mixed histology, <i>n</i> (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Performance Status/Grading System	NS	NS	ECOG 0–3	ECOG 1–3	–
PS0–PS1	NS	NS	7 (50%)	NS	–
PS2–PS3	NS	NS	7 (50%)	NS (PS1-2:16 (80%) PS3: 4 (20%))	–
Assessment of response					
Treatment schedule	Carboplatin-4epiADM	ADMs./ADMts	GEMOX	ADM + CDDP /CLF + ADM + CDDP	–
Classification system response	OMS	EORTC-99	RECIST	NS	–
CR + PR, <i>n</i> , (RR by study)	6 (43%)	1 (4.5%)	8 (57%)	4 (20%)	19 (27.1%)
RR	43%	8 (36.3%)	12 (86%)	10 (50%)	43 (61.4%)
Clinical benefit (CB)	13 (93%)	0 (0)	1 (7)	0 (0)	2 (2.8%)
CR, <i>n</i> (% by study)	1 (7)	0 (0)	1 (7)	0 (0)	17 (24.2%)
% Total	(36)	(4.5)	(50)	(20)	(34.2%)
PR, <i>n</i> (% by study)	5 (36)	7 (31.8)	4 (29)	6 (30)	24 (34.2%)
% Total	(50)	(31.8)	(29)	(30)	(34.2%)
SD, <i>n</i> (% by study)	7 (50)	11 (50)	2 (14)	10 (50)	24 (34.2%)
% Total	(50)	(50)	(14)	(50)	(34.2%)
PD, <i>n</i> (% by study)	1 (7)	3 (13.6%)	0 (0%)	0 (0%)	3 (4.2%)
% Total	(7)	(13.6%)	(0%)	(0%)	(4.2%)
NA, <i>n</i> (% by study)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

CDT-RAI, differentiated non-medullary refractory radioactive iodine thyroid cancer; PS, performance status; NS, unspecified; ADM, adriamycin; CDDP, cisplatin; GEMOX, gemcitabine + oxaliplatin; CLF, cyclophosphamide; CR, complete response; PR, partial response; RR, response rate = CR + PR/total number of patients; SD, stable disease; CB, clinical benefit = CR + PR + SD/total number of patients; PD, progression disease; NA, not assessable.

Santini et al. 2002, Spano et al. 2012) (Table 10). In addition, the probability of survival of all individuals with CDT-RTI (54 patients) was calculated. Median survival was estimated at 18 months (95% CI 0–37.5) and univariate survival analysis was performed in relation to age (>/<45 years), sex (M/F), histological type (papillary/follicular), number of metastases (1 or 2/>2), metastatic site, monotherapy scheme versus combination chemotherapy and if the treatment was established before or after the year 2000. We found a statistically significant difference in favour of combination chemotherapy versus monotherapy (15.2 versus 35.6 months; $P=0.001$) (Fig. 4) and in those which were treated after the year 2000 compared with those treated previously (41.2 versus 13 months, $P=0.000$). In multivariate analysis, the date of patients' treatment (before or

after 2000) was the only independent variable in relation to survival. In another three studies, there were observed differences in the median survival between responders to the treatment (from 11+ to 36 months) and non-responders (between 4 and 19 months) studies (Gottlieb & Hill 1974, Santini et al. 2002, Argiris et al. 2008). Two studies expressed these differences as the average, in 15.5 versus 3 months and 19 versus 5.4 months respectively (Benker & Reinwein 1983, Hoskin & Harmer 1987).

Discussion

In 2012, the estimated incidence of thyroid cancer in Spain was 2059 cases (3.4/100 000), with a mortality of 286 cases (0.3/100 000) (Ferlay et al. 2015). Among them, well-differentiated thyroid cancer is the most frequent and it

Table 6 Response rate: individual response data in CDT-RTI

Study, year	No. patients with DTC (% overall study)	NA (n)	CR (n)	PR (n)	CR+PR (n)	SD+PD (n)
Monotherapy						
Gottlieb & Hill (1974)	15 (50%)	0	0	5	5	10
Schlumberger & Parmentier (1989)	7 (41%)	0	0	0	0	7
Matuszczyk <i>et al.</i> (2008)	19 (100%)	0	0	1	1	18
Combination therapy						
Benker <i>et al.</i> (1977)	8 (38%)	1	2	1	3	4
Benker & Reinwein (1983)	21 (50%)	2	0	7	7	12
Bukowski <i>et al.</i> (1983)	5 (45%)	0	0	1	1	4
Shimaoka <i>et al.</i> (1985)	35 (42%)	0	2	6	8	27
Williams <i>et al.</i> (1986)	7 (32%)	0	0	1	1	6
De Besi <i>et al.</i> (1991)	8 (36%)	0	0	3	3	5
Scherübl <i>et al.</i> (1990)	8 (40%)	2	0	0	0	6
Santini <i>et al.</i> (2002)	14 (100%)	0	1	5	6	8
Argiris <i>et al.</i> (2008)	15 (88%)	0	0	1	1	14
Spano <i>et al.</i> (2012)	14 (100%)	0	1	7	8	6
Total	176 (100%)	5	6	38	44	127
		(2.8%)	(3.4%)	(21.6%)	(25%)	(72.15%)

CR, complete response; PR, partial response; RR, response rate=CR+PR/total number of patients; SD, stable disease; PD, progressive disease; NA, not assessable.

does not usually compromise the survival of patients who suffer from it, except for a small proportion that will become resistant to radioactive iodine treatment (Durante *et al.* 2006). The low casuistic could be one of the reasons why the research on chemotherapy of this condition has been scarce. Just 16 series of patients have been identified in 40 years; these series also had a high bias risk and did not achieve a total of 250 patients with well-differentiated tumours. Notwithstanding, in the current literature, there is no doubt in accepting as something sufficiently investigated, that chemotherapy has little function in the treatment of these patients.

Studies published in the 1970s, 80s, and 90s included all types of histology (well-differentiated tumours, in proportions between 15 and 50%, medullary and anaplastic) (Gottlieb & Hill 1974, Bukowski *et al.* 1983, Shimaoka

et al. 1985, Williams *et al.* 1986, Hoskin & Harmer 1987, De Besi *et al.* 1991). Anaplastic ones were excluded in the 1990s (Schlumberger & Parmentier 1989, Droz *et al.* 1990, Scherübl *et al.* 1990). From 2002 onward, four small studies were published, which only selected patients with well-differentiated tumours (Santini *et al.* 2002, Matuszczyk *et al.* 2008, Spano *et al.* 2012, Hussein *et al.* 2013). Therefore, it seems difficult to draw conclusions applicable to our current knowledge of series prior to the 2000s, given the differences that are already known in the behaviour of thyroid neoplasms and depending on the histology. Considering the data of these last studies seems insufficient.

Heterogeneity in selection adds to the diversity of received treatment and response assessment techniques, which have varied through the decades. In the 1970s,

Table 7 Response rate: individual response data relative to histological subtype^a

Total data	Patients (n) %	NA (n) %	CR (n) %	PR (n) %	CR+PR (n) RR	SD+PD (n) %
DTC-RTI	176	5	6	38	44	127
	100%	2.84%	3.4%	21.59%	25%	72.15%
Papillary type	39	1	1	9	10	28
	100%	2.56%	2.56%	23.07%	25.64%	71.79%
Follicular type	58	2	3	16	19	37
	100%	3.44%	5.1%	27.58%	32.75%	63.79%

CDT-RTI, differentiated non-medullary refractory radioactive iodine thyroid cancer; NA, not assessable; CR, complete response; PR, partial response; RR, response rate=CR+PR/total number of patients; SD, stable disease; PD, progressive disease.

^aIn seven patients the papillary or follicular histological subtype is not reported.

Table 8 Clinical benefit of chemotherapy according to the therapeutic scheme

Study	n	NA (n) %	CR+PR (n) RR (%)	SD (n) %	CB (n) %	PD (n) %
RCT	84	2 2.3%	18 21.4%	22 26.1%	40 48.7%	42 50%
Monotherapy, ADM or CDDP	93	6 6.4% (0–13.6%)	14 15% (0–37%)	26 27.9% (23–32%)	40 43% (32–63.3)	47 51% (37–64)
ADM+ cisplatin	69	1 1.4% (0–4.5%)	14 20.2% (0–42.8%)	31 44.9% (24–55%)	45 65.2% (50–81%)	23 33.3% (25–50)
ADM without cisplatin	102	10 9.8% (0–14.2%)	24 23.5% (0–36.3%)	36 35.2% (8–59%)	60 58.8% (25–67)	32 31.3% (19–67)
Others	57	2 3.5% (0–16.6%)	15 26.3% (6–57%)	20 35% (17–50%)	35 61.4% (25–93%)	20 35% (7–58%)
Total	405	21 5.1% (0–14.2%)	85 20.9% (0–57%)	135 33.3% (8–59%)	220 54.3% (25–93%)	164 40.4%

NA, not assessable; CR, complete response; PR, partial response; RR, response rate=CR+ PR/total number of patients; SD, stable disease; CB, clinical benefit= CR+PR+SD/total number of patients; PD, progressive disease; RCT, randomized clinical trial; ADM, adriamycin. For analysis of the CB three studies (Bukowski *et al.* (1983), Williams *et al.* (1986), Hoskin & Harner (1987)) were excluded as not providing data on SD and PD (rank of individual study results).

those most studied were adriamycin administered singly or in combination without cisplatin and in any type of histology. Studies with cisplatin-adriamycin combination have been published since 1985 (Williams *et al.* 1986, Scherübl *et al.* 1990, De Besi *et al.* 1991, Hussein *et al.* 2013), and in the twenty-first century, already three studies have assessed treatment with more modern drugs and techniques (Santini *et al.* 2002, Argiris *et al.* 2008, Spano *et al.* 2012). In recent years and in well differentiated non-medullary tumours, series have been published with few patients assessing the efficacy of adriamycin (Matuszczyk *et al.* 2008), adriamycin combined with cisplatin (Hussein *et al.* 2013), GEMOX (Spano *et al.* 2012) epiadriamycin combined with carboplatin (Santini *et al.* 2002) in conditions of hypothyroidism and the combination of adriamycin with alpha interferon

(Argiris *et al.* 2008) with very different results (RR between 6 and 50%). None of the studies that assessed monotherapy achieved CR, whose rate was 3.2% (2–6%) for treatments with combinations. Although limited, the possibility of obtaining CR seems important, due to the fact that they have been described as long-lasting and with a probable relationship to the survival (Bukowski *et al.* 1983, Shimaoka *et al.* 1985, Argiris *et al.* 2008). Currently, a relation between PS and chemotherapy response is recognised, although the inclusion in clinical trials of patients with PS > 2 is rare. In this series, nearly 40% of the patients presented a PS ≥ 2, a very high proportion in comparison to those published in the DECISION study (3.4%) (Brose *et al.* 2014). Therefore, better results could be for the treatment with chemotherapy in patients with better PS. Although there does seem to be sufficient

Table 9 Clinical benefit to chemotherapy according to histological subtype^a

DTC-RTI	Patients (n) %	NA (n) %	CR (n) %	PR (n) %	CR+PR (n) RR	SD (n) %	CR+PR+SD (n) CB	PD (n) %
Total group	129 100%	5 1.61%	4 3.1%	30 23.25%	34 26.35%	49 37.98%	83 64.34%	41 31.78%
Papillary type	37 100%	1 2.7%	1 2.7%	9 24.32%	10 27.02%	20 54.05%	30 81.08%	6 16.21%
Follicular type	55 100%	2 3.63%	3 5.45%	15 27.27%	18 32.72%	18 32.72%	36 65.45%	17 30.9%

CDT-RTI, differentiated non-medullary refractory radioactive iodine thyroid cancer; NA, not assessable; CR, complete response; PR, partial response; RR, response rate=CR+PR/total number of patients; SD, stable disease; PD, progression disease.

^aIn seven patients the papillary or follicular histological subtype was not reported.

Table 10 Overall survival

Study	n	Median survival (months)	Mean survival (months)
Gottlieb & Hill (1974)	30	NS	NS
Benker & Reinwein (1983)	52	NS	9 ^a
Bukowski <i>et al.</i> (1983) ^b	11	4 95% CI (2.4–5.5) Rank (2–60+)	9 95% CI (0–18.5) Rank (2–60+)
Williams <i>et al.</i> (1986)	28	NS	11.7 ^a
Hoskin & Harmer (1987) ^b	29	10 95% CI (3.8–16.1) Rank (1–54)	11.9 ^a 14.2 95% CI (8.3–20) Rank (1–54)
De Besi <i>et al.</i> (1991)	22	16 ^a Rank (2–57)	NS
Schlumberger & Parmentier (1989) ^b	17	13 95% CI (11.8–14.1) Rank (1–26+)	12.3 95% CI (0–18.5) Rank (1–26+)
Droz <i>et al.</i> (1990) Study A	12	NS	12 ^a Rank (1–46)
Droz <i>et al.</i> (1990) Study B	22	NS	20 ^a Rank (3–60)
Droz <i>et al.</i> (1990) Study C	19	NS	14 ^a Rank (1–56)
Droz <i>et al.</i> (1990) Study D	12	NS	14 ^a Rank (2–48)
Droz <i>et al.</i> (1990) Study E	7	NS	7 ^a Rank (4–13)
Argiris <i>et al.</i> (2008)	17	26.4 95% CI (6.7–46.1)	NS
Santini <i>et al.</i> (2002) ^b	14	Not reached Rank (9–41)	34.7 95% CI (27.7–41.8) Rank (9–41)
Spano <i>et al.</i> (2012) ^b	14	Not reached Follow-up: 19.8	44.3 95% CI (30.3–58.4) Rank (2–62+)
Hussein <i>et al.</i> (2013)	20	NS	9 ^a Rank (6–12)

NS, not specified.

^aStatistics, are expressed as mean or median based on the data provided in the different studies.

^bSurvival probability calculated based on individual survival data and status of patients at follow-up.

evidence of chemotherapy's effectiveness in terms of the RR and the response's quality, it could be even superior to sorafenib. In particular, this should be considered because the significance of the response to chemotherapy in advanced radioactive iodine refractory thyroid carcinoma was never assessed properly, and few studies have been performed with modern methodology and chemotherapy.

Extracting conclusions from the PFS data is also difficult, because they are described scarcely and, generally, as statistics and not as probabilities, thus comparison with actual results is complex (Argiris *et al.* 2008, Spano *et al.* 2012, Hussein *et al.* 2013). Just one small

study, Spano *et al.* (2012) provided individual data for the PFS and the progression status at the end of the monitoring, the median PFS was 10 months with 95% CI of 4.1–16.2, similar to the one achieved with sorafenib (Brose *et al.* 2014). As for the chemotherapy effect on the survival, data is insufficient and, due to the variable course of these tumours, with patients who stay several years with disseminated disease, the evaluation of

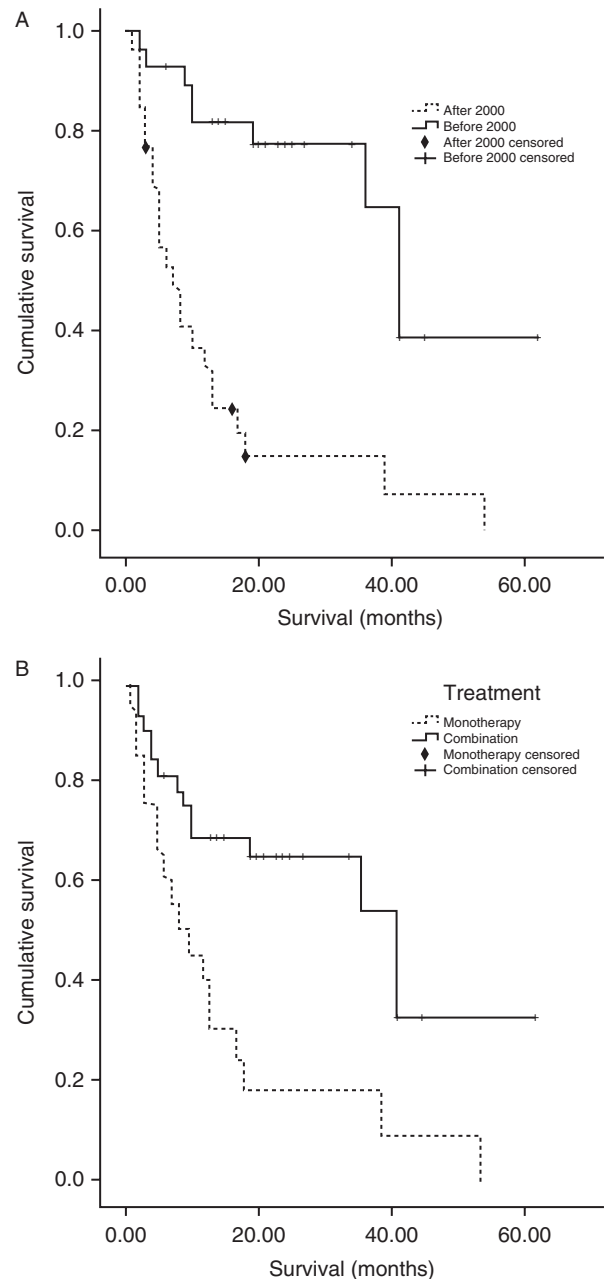


Figure 4 Survival Curves for DTC treatment: (A) before or after 2000 and (B) monotherapy vs combination.

patients' characteristics and the evolutionary moment of departure must be very equilibrated and defined for it to be comparable.

Up to now, a treatment which increases the survival of these patients has not been developed, even the cross-over in the trial may indicate that patients can be treated at more advanced stages of the disease without reducing overall survival. Otherwise, if the treatment just achieves an increase in the PFS, this must guarantee a good quality of life. The review of the referred toxicity with the chemotherapy should be cautious. The accumulated experience with these agents and the improvement in supportive care has allowed alleviation and easing of many side effects. Thus, severe cardiotoxicity by adriamycin, almost unknown in the 1970s (Gottlieb & Hill 1974) and described in 10% of the series, has a current frequency of nearly <0.1% when an oncological practice is performed (e.g. calculation of the cumulative dose of adriamycin, cisplatin and good hydration) (Matuszczyk et al. 2008). As for other toxicities, they are generally less frequent and current. Comparing toxicities referred to in an old study (Gottlieb & Hill 1974) and in a modern one (Matuszczyk et al. 2008) with the same drug and doses, they results were, respectively, neutropenia 80% versus 10%, alopecia 77% versus 42%, nausea and vomiting 53% versus 23%, thrombocytopenia 13% versus 0%, in all its grades. Taking into account that each scheme has its toxicological profile, in general, this toxicity is considered to be acceptable (Matuszczyk et al. 2008, Spano et al. 2012). One of the most concerning problems about sorafenib and lenvatinib is its toxicity (approved for the treatment of this disease because they increase PFS without affecting survival). The DECISION (Brose et al. 2014) and SELECT (Schlumberger et al. 2015) studies describe frequent and unpleasant toxicities (foot-hand syndrome 76.3% and 31.8%, diarrhea 68.6% and 59%, alopecia 67% and 11.1%, and about 50% of patients presented rash and desquamation, asthenia, weight loss, nausea and hypertension) as well as severe effects (the most frequent grade 3–4 toxicities: foot-hand syndrome 20% and 3.4%, HTA 9.7% and 42%, and about 5% and 8% for diarrhea, rash, asthenia, dyspnoea and weight loss). In addition, in the SELECT study it was reported that 97% of the cases presented side effects, 76% with toxicity greater than or equal to grade 3 and 2.3% of toxic deaths (Schlumberger et al. 2015). This toxicity seems much higher than those referred to for chemotherapy, although some may decline over time (Worden et al. 2015), with the exception of adriamycin in association with IF, a very toxic scheme with little efficacy (Argiris et al. 2008).

We considered that there is solid data that seems to confirm the efficacy of sorafenib and lenvatinib, but due to the fact that the survival increase has not been demonstrated, there is not a clear clinical benefit or a decrease in the genesis of side effects, besides having been associated with a notable increase in the cost. Therefore, chemotherapy should be studied under the right conditions, in multicentre randomized studies that select patients with well-differentiated tumours with good PS and where the primary purpose is survival with assessment of quality of life. Whether the efficacy of chemotherapy is demonstrated or not, interesting lines of research could be established that could help to improve the actual results for patients with thyroid cancer as the sequential therapy with chemotherapy and/or other drugs, among others.

Conclusions

The effectiveness of chemotherapy in well-differentiated radioiodine refractory thyroid cancer is not well established, although there is evidence that indicates it could have greater activity with modern drugs and in patients with better PS. Given the scant advance from the treatment of these patients, we considered that well-designed studies should be performed which analyse the efficacy and security of chemotherapy treatment with more modern drugs.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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