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Tan A, Xia N, Gao F, Mo Z, Cao Y

Tan A, Xia N, Gao F, Mo Z, Cao Y.
Angiogenesis-inhibitors for metastatic thyroid cancer.
Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD007958.
DOI: [10.1002/14651858.CD007958.pub2](https://doi.org/10.1002/14651858.CD007958.pub2).

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[Intervention Review]

Angiogenesis-inhibitors for metastatic thyroid cancer

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Editorial group: Cochrane Metabolic and Endocrine Disorders Group.

Publication status and date: New, published in Issue 3, 2010.

Citation: Tan A, Xia N, Gao F, Mo Z, Cao Y. Angiogenesis-inhibitors for metastatic thyroid cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD007958. DOI: [10.1002/14651858.CD007958.pub2](https://doi.org/10.1002/14651858.CD007958.pub2).

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ABSTRACT

Background

Systemic cytostatic therapies for advanced, metastatic thyroid carcinomas have been poorly effective. Tumor growth and metastasis depend on blood supply and blood vessel formation (angiogenesis). Therefore, inhibition of angiogenesis may represent a promising target for cancer therapy.

Objectives

To evaluate the benefits and risks of angiogenesis-inhibitors for metastatic thyroid cancer when given alone, or in combination with chemotherapy or radiotherapy.

Search methods

We searched *The Cochrane Library* (2009, Issue 2), MEDLINE (January 2000 to May 2009) and EMBASE (January 2000 to May 2009) databases and abstracts published in annual proceedings for evidence. Attempts were made to identify studies from references in potentially relevant trials. We also searched for ongoing trials.

Selection criteria

We planned to include randomized controlled trials that compared angiogenesis-inhibitors with other treatments, no treatment, or placebo in participants who had pathologically confirmed advanced thyroid cancer.

Data collection and analysis

Two authors independently evaluated the search results against the selection criteria. Data extraction and risk of bias assessment were not performed because there were no studies that could be included.

Main results

We did not identify any studies which met our full inclusion criteria.

Authors' conclusions

There is currently no reliable evidence available from randomized controlled trials regarding the benefits and harms of the use of angiogenesis-inhibitors for treating advanced thyroid cancer. Several trials are ongoing.

PLAIN LANGUAGE SUMMARY

Angiogenesis-inhibitors for metastatic thyroid cancer

Angiogenesis-inhibitors for metastatic thyroid cancer (Review)

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There is currently no reliable evidence from randomized controlled trials demonstrating that the benefits of angiogenesis-inhibitors outweigh their risks in treating advanced thyroid cancer. Angiogenesis (that is blood supply of tumors and new blood vessel formation in tumors) plays an important role in tumor growth and metastasis. Currently, four randomized controlled trials are ongoing. Despite the potential benefits of angiogenesis-inhibitors, various undesirable side effects have been reported. These include rash, diarrhea, fatigue, nausea, proteinuria, stomatitis or mucositis, and hypertension. We will update this review as data from the ongoing trial become available.

BACKGROUND

Description of the condition

Thyroid cancer is the most common malignant tumor of the endocrine system. The incidence of thyroid cancer has increased remarkably in recent years, from 4.9 cases per 100,000 in 1975 to 9.8 per 100,000 in 2004 in the USA ([National Cancer Institute 2008](#)). According to recent data, in 2008, an estimated 37,340 cases of thyroid cancer will have been diagnosed and 1590 people will have died from this disease in the USA ([Am Cancer Soc 2008](#)). Thyroid cancer rises from two types of cells, follicular cells and parafollicular cells or C cells. The former gives rise to differentiated and undifferentiated types of cancer. Differentiated thyroid cancer (DTC) mainly consists of papillary and follicular subtypes, accounting for 85% to 95% of cases. The undifferentiated form includes anaplastic thyroid carcinoma (ATC), known as one of the most aggressive and chemotherapy-resistant tumors in human beings ([Carling 2005](#)). Parafollicular or C cells are the cells of origin for medullary thyroid carcinoma (MTC), which may be familial or sporadic. The prognosis of thyroid cancer varies widely. For well-differentiated and encapsulated tumors, the 10-year overall survival rates are reported to reach 91%. For patients with extrathyroidal manifestations, the 10-year overall survival rates drop to 45%. The reported incidence of extrathyroidal manifestations of well-differentiated thyroid carcinoma ranges from 6% to 13%. Adverse prognostic factors include age, tumor histology, primary tumor size and distant metastasis ([Andersen 1995](#); [Hay 2002](#); [Randolph 2006](#); [Shah 1992](#)). The ATC has a 10-year median survival of only 13% ([Gilliland 1997](#)).

Description of the intervention

The mainstay of treatment of thyroid carcinoma is surgery, varying from less aggressive surgery such as unilateral lobectomy to total thyroidectomy with lymph node dissection. However, it is limited in terms of locally invasive or distant metastatic thyroid carcinoma. For locally invasive thyroid carcinoma, complete resection of critical structures such as nerves, trachea, and oesophagus with negative margins is associated with significant morbidity, seriously affecting the quality of life of patients. Therefore, other treatments are considered for this condition, which mainly include radiotherapy and chemotherapy. Radiotherapy consists of external radiotherapy and radioiodine (RAI). In the case of local invasion and risk of residual microscopic disease after surgery, external radiation provides an alternative. The addition of external radiation improves the locoregional control as well as local recurrence, particularly after incomplete surgical resection or in the presence of extracapsular tumor extension. In addition, higher doses are also associated with greater late complications ([Phlips 1993](#); [Tubiana 1985](#)). Radioiodine, in the form of iodine-131, is another form of radiotherapy in the treatment of thyroid carcinoma, which causes cytotoxicity by the emission of radiation. Radioiodine has remained the standard treatment for locally advanced differentiated thyroid carcinoma when combined with surgery. It also continues to be the initial treatment for distant metastatic disease and can produce 5-year overall survival rates of around 50% ([Kebebew 2006](#)). However, patients with locally invasive thyroid cancer are more likely to have aggressive histologic variants that may not effectively concentrate RAI ([Kasperbauer 2004](#); [Mattavelli 2007](#)). Moreover, RAI itself might be associated with rare but serious adverse events, including pulmonary fibrosis and secondary malignant diseases such as acute myelogenous leukemia ([Sisson 1996](#)). Chemotherapy, as

another choice especially for patients with iodine resistance and contraindications, however, is not as effective as anticipated, with all subtypes demonstrating extremely low response rates, sometimes less than 1% ([Shimaoka 1985](#)).

In summary, well-differentiated papillary and follicular carcinomas can be effectively treated by surgery followed by radioiodine therapy. However, poorly-differentiated tumors or unresectable follicular cell-derived tumors together with C cell-derived medullary carcinomas usually fail with traditional treatment and have an unfavourable prognosis. Novel therapeutic strategies that are based on an understanding of cancer biology have provided new opportunities for the treatment of these thyroid cancers.

Angiogenesis refers to the growth of new blood vessels from pre-existing vasculature, which is necessary for the supply of oxygen, nutrients, growth factors, hormones, proteolytic enzymes and dissemination of tumor cells to distant sites. It is a highly complex, dynamic process regulated by a number of pro- and anti-angiogenic molecules. When pro-angiogenic factors outweigh anti-angiogenic factors, endothelial cells become activated from their normal quiescent state. This is known as the 'angiogenic switch' ([Bergers 2003](#)). Physiological angiogenesis is only transiently observed during embryogenesis, wound healing and reproductive functions in adults. In contrast, abnormal angiogenesis takes place in certain chronic diseases, such as diabetes, psoriasis, rheumatoid arthritis and malignant tumors ([Fidler 1994](#); [Folkman 1990](#)). The dependence of tumor growth on the development of new blood vessels is now a well-established aspect of cancer biology ([Folkman 1971](#)). Tumor blood vessels show perivascular detachment, vessel dilation, and irregular shape. It is believed that tumor blood vessels are not smooth like normal tissues and are not ordered sufficiently to give oxygen to all of the tissues ([Burri 2004](#)). Endothelial precursor cells are organized from bone marrow, which are then integrated into the growing blood vessels ([Folkman 1987](#)). Angiogenesis is crucial to tumor initiation, survival and metastasis. Tumors cannot grow beyond 1 to 2 mm in size without angiogenesis and then metastasis. Besides, some clinicians believe that angiogenesis serves as a waste pathway, taking away the biological end products put out by rapidly dividing cancer cells. Tumor-related angiogenesis is a multi-step process initiated through the activity of various pro-angiogenic factors or stimuli secreted by tumor cells and host components such as macrophages, lymphocytes and kidney cells. Of these pro-angiogenic factors, vascular endothelial growth factor (VEGF) is predominant, which stimulates the proliferation of endothelial cells and the formation of new blood vessels via interaction with the transmembrane endothelial VEGF receptor ([Rosen 2002](#)). Moreover, it was discovered that cancerous cells stop producing the anti-VEGF enzyme protein kinase G, which, in more cells, limits beta-catenin which solicits angiogenesis ([ScienceDaily 2007](#)). Increased expression of VEGF has been found in thyroid carcinoma compared with normal thyroid tissue. A number of angiogenesis-inhibitors such as axitinib ([Cohen 2007](#)), sorafenib ([Gupta 2007](#)), vandetanib ([Wells 2007](#)) and combretastatin A4 phosphate (CA4P) ([Cooney 2006](#)) have been investigated in the treatment of thyroid cancer, with encouraging outcomes. Angiogenesis-inhibitors can be classified as direct, indirect or mixed inhibitors according to their mode of action ([Gasparini 2005](#)):

- direct angiogenesis-inhibitors, inhibiting the endothelial cells involved in the malignant disease to proliferate, migrate, or form new blood vessels;
- indirect angiogenesis-inhibitors, interfering with the production of angiogenic factors by malignant, stromal or inflammatory cells or extracellular processes;
- mixed angiogenesis-inhibitors, targeting both tumor endothelial and malignant cells, such as multi-targeting kinase inhibitors.

Adverse effects of the intervention

In general, angiogenesis-inhibitors usually have only mild side effects and are not toxic to most healthy cells as compared to cytotoxic agents. Some adverse effects have been reported as follows:

- sorafenib: adverse effects include desquamating rash often appearing on the hands and gastrointestinal symptoms (Gupta 2007);
- vandetanib: adverse effects include rash (73%), diarrhea (67%), fatigue (57%) and nausea (53%) (Wells 2007);
- axitinib: adverse effects include fatigue (37%), proteinuria (27%), stomatitis or mucositis (25%), diarrhea (22%), hypertension (20%) and nausea (18%) (Cohen 2007).

How the intervention might work

Most of the angiogenesis-inhibitors developed to treat thyroid cancer are mixed angiogenesis-inhibitors, which block tumor angiogenesis and target vascular endothelial cells, as well as tumor endothelial and malignant cells. Anti-angiogenic therapy presents various advantages when compared with conventional therapy. First, normal endothelial cells are quiescent under physiological conditions while tumor endothelial cells are actively proliferating and migrating (Longo 2002). Secondly, endothelial cells are genetically more stable than cancer cells. This genomic stability confers an advantage to targeting endothelial cells using anti-angiogenic therapy, as compared to chemotherapy directed at cancer cells, which rapidly mutate and acquire 'drug resistance' to treatment (Rak 1996). Thirdly, tumor endothelium can be easily reached by anti-angiogenic agents given via systemic administration.

Why it is important to do this review

Considering the limitation of surgical treatment, the lack of substantial effective chemotherapy and sensitivity to iodine radiation, as well as poor prognosis in advanced thyroid carcinoma of all subtypes, the early results achieved by angiogenesis-inhibitor therapy are promising. Clinical trials have been designed to evaluate the targeted therapy in thyroid cancer. Due to the relatively low incidence of thyroid cancer, the sample size of primary studies is often small, thus having low power to evaluate innovative therapeutic approaches. Therefore, a systematic review and meta-analysis of existing data will provide more accurate guidance for treatment decisions.

OBJECTIVES

To evaluate the benefits and risks of angiogenesis-inhibitors for metastatic thyroid cancer when given alone, or in combination with chemotherapy or radiotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Those with pathologically confirmed metastatic thyroid cancer.

Types of interventions

Intervention

- (1) angiogenesis-inhibitors;
- (2) angiogenesis-inhibitors plus chemotherapy;
- (3) angiogenesis-inhibitors plus radiotherapy.

Control

- (1a) no treatment;
- (1b) placebo;
- (2) chemotherapy;
- (3) radiotherapy.

Types of outcome measures

Primary outcomes

- overall survival (OS);
- progression-free survival (PFS);
- event-free and disease-free survival (EFS, DFS).

Secondary outcomes

- adverse events;
- objective response rate (ORR);
- health related quality of life (measured by a validated instrument);
- costs.

Covariates, effect modifiers and confounders

Disease stage, prognostic factors (e.g. age, number of metastatic sites).

Timing of outcome measurement

Long-term for overall survival; medium-term for progression-free survival, event-free and disease-free survival.

Search methods for identification of studies

Electronic searches

We searched the following sources for the identification of trials:

- *The Cochrane Library* (Issue 2, 2009);
- MEDLINE (from January 2000 until May 2009);
- EMBASE (from January 2000 until May 2009).

We also searched databases of ongoing trials: 'Current Controlled Trials' (www.controlled-trials.com - with links to other databases of ongoing trials).

For detailed search strategies please see under [Appendix 1](#).

Where additional keywords were identified during any of the searches, we planned to incorporate these into the search strategies. There were no language restrictions on the searches or studies to be considered for inclusion.

Searching other resources

We tried to identify additional studies by searching the reference lists of included trials and (systematic) reviews, meta-analyses and health technology assessment reports found.

We handsearched published abstracts from conference proceedings from the European Society for Medical Oncology 2000 to 2008 (published in the *Annals of Oncology*); the European Council for Clinical Oncology 2000 to 2008 (published in the *European Journal of Cancer*), and the American Society for Clinical

Oncology 2000 to 2008. In addition, experts in the field and manufacturers of relevant drugs were asked to provide details of outstanding clinical trials and any relevant unpublished material.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two authors (Aihua Tan and Ning Xia) independently scanned the abstract, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Interrater agreement for study selection was planned to be measured using the kappa statistic ([Cohen 1960](#)). Differences would have been marked and if these studies were later on included, we planned to study the influence of the primary choice by means of a sensitivity analysis. Where differences in opinion existed, they would have been resolved by a third party. If resolving disagreement was not possible, the article was planned to be added to those 'awaiting assessment' and authors were contacted for clarification. An adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection ([Liberati 2009](#)) is attached ([Figure 1](#)).

Figure 1. Aadapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart of study selection

Data extraction and management

For studies that fulfilled the inclusion criteria, it was planned that two authors (Aihua Tan and Ning Xia) would independently abstract relevant population and intervention characteristics using standard data extraction templates. Any disagreements were to be resolved by discussion, or if required, by a third party. Any relevant missing information on the trial was planned to be sought from the original author(s) of the article, if required.

Dealing with duplicate publications

In the case of duplicate publications and companion papers of a primary study, we wanted to maximise the yield of information by simultaneous evaluation of all available data. In cases of doubt, the original publication (usually the oldest version) would have obtained priority.

Assessment of risk of bias in included studies

Two authors (Aihua Tan and Ning Xia) planned to assess each trial independently using the Cochrane Collaboration's risk of bias tool (Higgins 2008). Possible disagreement was to be resolved by consensus, or with consultation of a third party in case of disagreement. We wanted to explore the influence of individual bias criteria in a sensitivity analysis (see under 'sensitivity analyses'). Interrater agreement for key bias indicators (e.g. allocation concealment, incomplete outcome data) was planned to be calculated using the kappa statistic (Cohen 1960). In cases of disagreement, the rest of the group would have been consulted and a judgement made based on consensus.

Measures of treatment effect

Dichotomous outcomes were planned to be expressed as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI).

Continuous outcomes would be expressed as mean differences with 95% CI. Time-to-event outcomes would be expressed as hazard ratios (HR) with 95% CI.

Dealing with missing data

We wanted to obtain relevant missing data from authors, if feasible. Evaluation of important numerical data such as screened, randomized patients as well as intention-to-treat (ITT) and per-protocol (PP) population would have been carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals would have been investigated. Issues of missing data and techniques to handle these (for example, last observation carried forward (LOCF)) were planned to be critically appraised.

Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity, study results would not be combined by means of meta-analysis. We wanted to identify heterogeneity by visual inspection of the forest plots, by using a standard χ^2 test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity was planned to be specifically examined with the I^2 statistic (Higgins 2002), where I^2 values of 50% and more indicate a substantial level of heterogeneity (Higgins 2003). When heterogeneity was found, we planned to attempt to determine potential reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We wanted to use funnel plots to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2001). Therefore, we planned to carefully interpret results (Lau 2006).

Data synthesis

Data were planned to be summarised statistically if they were available, sufficiently similar and of sufficient quality. Statistical analysis would have been performed according to the statistical guidelines referenced in the newest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Subgroup analysis and investigation of heterogeneity

We wanted to carry out subgroup analyses if one of the primary outcome parameters demonstrated statistically significant differences between intervention groups. In any other case, subgroup analyses would have been clearly marked as a hypothesis generating exercise.

The following subgroup analyses were planned:

- different types, doses and delivery modes of angiogenesis-inhibitors;
- the use of angiogenesis-inhibitors alone or in combination with chemotherapy or with radiotherapy;
- types of thyroid cancer.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analysis excluding unpublished studies;

- repeating the analysis taking account of risk of bias, as specified above;
- repeating the analysis excluding any very long or large studies to establish how much they dominated the results;
- repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We also wanted to test the robustness of the results by repeating the analysis using different measures of effect size (relative risk, odds ratio etc.) and different statistical models (fixed-effect and random-effects models).

RESULTS

Description of studies

We found no studies meeting all the inclusion criteria. Four RCTs that compare angiogenesis-inhibitors with other treatments in participants with advanced thyroid cancer are ongoing and no data are currently available (for details see [Characteristics of ongoing studies](#)). Fifteen trials evaluating angiogenesis-inhibitors for advanced thyroid cancer were non-randomized, phase II studies (for details see [Characteristics of excluded studies](#)).

Results of the search

The initial search led to 832 references, 19 potentially relevant trials were identified ([Figure 1](#)).

Included studies

No studies were suitable for inclusion. Four studies are ongoing ([NCT00410761](#); [NCT00507429](#); [NCT00537095](#); [NCT00984282](#)).

Excluded studies

Fifteen studies were excluded, these were all non-randomized phase II trials (Ahmed 2008; Ain 2007; Ain 2008; Cohen 2008a; Cohen 2008b; Cooney 2006; de Groot 2007; Goulart 2008; Gupta-Abramson 2008; Haddad 2008; Kloos 2009; Pennell 2008; Ravaud 2008; Schlumberger 2009; Sherman 2008).

Risk of bias in included studies

No data were available for evaluation.

Effects of interventions

Since no studies were included, we could not evaluate the effects of the intervention.

DISCUSSION

Summary of main results

A summary of recent non-randomized, single group, phase II trial results of angiogenesis-inhibitors in thyroid cancer is shown in [Appendix 2](#). These are discussed in more detail below.

Three trials reported preliminary results of sunitinib in treating patients with refractory thyroid cancer. This was a heavily pretreated group of patients and sunitinib appeared to be active in both differentiated thyroid cancer (DTC) and medullary thyroid carcinoma (MTC). In the largest study of sunitinib in thyroid cancer to date, 43 patients with radioactive iodine-resistant disease were

treated with sunitinib, 50 mg daily, on a 4 weeks on/2 weeks off schedule. Among patients with differentiated carcinomas, 13% achieved a partial response (PR) and 68% had stable disease (SD). In contrast, 83% of patients with MTC had SD. Reported adverse effects were similar to those seen with sorafenib, including fatigue, diarrhea, palmar-plantar erythrodysesthesia (hand-foot syndrome), neutropenia, hypertension and thrombocytopenia.

Three trials evaluated the safety and efficacy of sorafenib in advanced thyroid cancer. In one trial with 41 papillary thyroid cancer (PTC) patients, six patients had a PR and 23 patients had SD longer than six months, the median PFS was 15 months. In the second trial with 30 included patients, there was an overall clinical benefit rate (PR plus SD) of 77% and a median PFS of 79 weeks. The third trial with 18 patients showed promising effects of sorafenib in advanced DTC and MTC despite dose reductions. Toxicity in all three trials included diarrhea, hand-foot syndrome and other skin toxicity, alopecia, hypertension, infection, and nausea.

Axitinib: One trial of axitinib showed it to be active in all histologic subtypes of advanced thyroid cancer with the most common grade 3 treatment-related adverse event being hypertension.

Motesanib diphosphate was reported to induce PRs in patients with advanced or metastatic DTC and SD in a significant proportion of MTC patients (81%) although the objective response rate was low (2%). The most common treatment-related adverse events were diarrhea, fatigue, hypothyroidism, hypertension, and anorexia.

In a study of gefitinib, no tumor responses were observed in 27 patients with radioiodine-refractory, locally advanced, or metastatic thyroid cancer, but falling thyroglobulin levels and prolonged SD were observed in a subset of patients. The most commonly reported toxicities were rash, diarrhea, nausea, and anorexia.

Imatinib therapy for metastatic MTC in another study yielded no objective responses and induced considerable toxicity (e.g. laryngeal swelling and recurrent nerve palsy).

In another trial, thalidomide conferred some therapeutic benefit in subsets of rapidly progressive, distantly metastatic thyroid cancer patients, with fatigue as the most frequent toxicity. For patients with locally advanced or metastatic hereditary MTC, vandetanib 100 mg made encouraging results in an open-label study. Lenalidomide was reported to be active in treating patients with distantly metastatic, rapidly progressive, and radioiodine-unresponsive thyroid carcinomas. Its grade 3 toxicities were hematological: 44% neutropenia and 22% thrombocytopenia. As the first tubulin-binding vascular disrupting agent tested in clinic, CA4P was demonstrated to be active in advanced anaplastic thyroid carcinoma (ATC) in a study of 18 patients, although no objective responses were observed. Therapy was well tolerated with mild to moderate nausea, vomiting, headache, and tumor pain.

According to the above non-randomized phase II studies, angiogenesis-inhibitors have shown a promising activity in advanced, metastatic thyroid cancer, especially in DTC. For the adverse events, most may be tolerated but some are lethal. Studies discussed here are still in early phases, and further large, randomized trials are required to better evaluate the effects or risks of angiogenesis-inhibitors in treating patients with advanced, metastatic thyroid cancer.

AUTHORS' CONCLUSIONS

Implications for practice

Since there is currently no evidence from RCTs to demonstrate that the benefits of angiogenesis-inhibitors outweigh their risks when used in the treatment of advanced, metastatic thyroid cancer, we can make no reliable recommendation about their use in clinical practice.

Implications for research

Well designed and executed RCTs with sufficient power are needed to evaluate the benefits and risks of angiogenesis-inhibitors compared to other therapies when used for metastatic thyroid carcinoma.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahmed 2008	Non-randomized phase II study
Ain 2007	Non-randomized phase II study
Ain 2008	Non-randomized phase II study
Cohen 2008a	Non-randomized phase II study
Cohen 2008b	Non-randomized phase II study
Cooney 2006	Non-randomized phase II study
de Groot 2007	Non-randomized phase II study
Goulart 2008	Non-randomized phase II study
Gupta-Abramson 2008	Non-randomized phase II study
Haddad 2008	Non-randomized phase II study
Kloos 2009	Non-randomized phase II study

Angiogenesis-inhibitors for metastatic thyroid cancer (Review)

Study	Reason for exclusion
Pennell 2008	Non-randomized phase II study
Ravaud 2008	Non-randomized phase II study
Schlumberger 2009	Non-randomized phase II study
Sherman 2008	Non-randomized phase II study

Characteristics of ongoing studies [ordered by study ID]

[NCT00410761](#)

Trial name or title	An efficacy study comparing ZD6474 to placebo in medullary thyroid cancer
Methods	Treatment, randomized, double-blind, placebo-controlled, parallel design, safety/efficacy study
Participants	Inclusion criteria: 1) patients must be greater than or equal to 18 years of age, 2) confirmed diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic medullary thyroid cancer, 3) presence of measurable tumor, 4) able to swallow medication.
Interventions	Drug: ZD6474 (vandetanib) once daily oral tablet
Outcomes	Primary outcome: progression-free survival; time to progression and death Secondary outcome: overall objective response rate, disease control rate, duration of response, overall survival
Starting date	November 2006
Contact information	AstraZeneca
Notes	This study is ongoing, but not recruiting participants

[NCT00507429](#)

Trial name or title	Study of combretastatin and paclitaxel/carboplatin in the treatment of anaplastic thyroid cancer
Methods	Treatment, randomized, open label, active control, parallel design, safety/efficacy study
Participants	Inclusion criteria: 1) patients must be greater than or equal to 18 years of age, 2) patients must have anaplastic thyroid carcinoma histologically or cytologically confirmed by a pathology review, 3) patients may have been refractory to or progressed during or after therapy, or relapsed within 6 months following initial combined modality therapy (usually including systemic chemotherapy and radiation) for regionally advanced disease, 4) where patients have received combined modality therapy for metastatic disease, systemic therapy is limited to one chemotherapy regimen that is clearly administered contiguously, 5) in patients having received prior radiation, 3 weeks must have elapsed since radiation and disease must be present beyond radiation ports.
Interventions	Drug: combretastatin A-4 phosphate (CA4P) 60 mg/m ² on days 1, 8 and 15 for 6 cycles Drug: paclitaxel 200 mg/m ² on day 1

NCT00507429 (Continued)

	Drug: carboplatin 6 AUC on day 1 following paclitaxel
Outcomes	Primary outcome: overall survival Secondary outcome: adverse events
Starting date	July 2007
Contact information	OXiGENE
Notes	This study is currently recruiting participants

NCT00537095

Trial name or title	Efficacy and safety of vandetanib in patients with metastatic papillary or follicular thyroid cancer
Methods	Treatment, randomized, double-blind, placebo-controlled, parallel design, safety/efficacy study
Participants	Inclusion criteria: 1) patients must be greater than or equal to 18 years of age, 2) previously confirmed histological diagnosis of locally advanced or metastatic papillary or follicular thyroid carcinoma, without anaplastic component; tumor sample available for centralized exploratory analysis, 3) presence of one or more measurable lesions at least 1 cm in the longest diameter by spiral CT scan or 2 cm with conventional techniques, 4) progressive disease following RAI131 or patient unsuitable for RAI131 after surgery, 5) serum TSH < 0.5 mU/L
Interventions	Drug: vandetanib 300 mg once daily oral dose
Outcomes	Primary outcome: progression free survival Secondary outcome: disease control rate; objective response rate; overall survival; adverse events
Starting date	October 2007
Contact information	AstraZeneca
Notes	This study is ongoing, but not recruiting participants

NCT00984282

Trial name or title	Nexavar versus placebo in locally advanced RAI-refractory differentiated thyroid cancer
Methods	Treatment, randomized, double-blind, placebo-controlled, crossover design, safety study
Participants	Inclusion criteria: 1) patients must be greater than or equal to 18 years of age, 2) locally advanced or metastatic differentiated thyroid cancer, 3) progression within 14 months, 4) RAI refractory Exclusion criteria: 1) prior anti-cancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF or VEGF receptors or other targeted agents, 2) prior anti-cancer treatment for thyroid cancer with use of chemotherapy (low dose chemotherapy for radiosensitization is allowed) or thalidomide or any of its derivatives
Interventions	Drug: nexavar (sorafenib, BAY43-9006) 400 mg administered orally, twice daily (approximately every 12 hours) Drug: placebo (2 tablets) administered orally, twice daily (approximately every 12 hours)

NCT00984282 (Continued)

Outcomes	Primary outcome: progression free survival Secondary outcomes: overall survival ; time-to-progression; disease control rate; overall response rate; duration of response
Starting date	October 2009
Contact information	Bayer Clinical Trials
Notes	This study is currently recruiting participants

APPENDICES

Appendix 1. Search strategies

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) or asterisk (*) stand for any character(s); the question mark (?) = to substitute for one or no characters; ab = abstract; adj = adjacent; ot = original title; pt = publication type; rn = Registry number or Enzyme Commission number; sh = MeSH; ti = title; tw = text word.

The Cochrane Library (Issue 2, 2009)

- #1 (thyroid near6 (cancer or tumor?r* or neoplasm* or metast*))
- #2 (metastatic and thyroid cancer)
- #3 MeSH descriptor Thyroid Neoplasms explode all trees
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Angiogenesis Inhibitors explode all trees
- #6 MeSH descriptor Angiostatic Proteins explode all trees
- #7 ((angiogenesis or neovascularisation*) near6 inhibitor*)
- #8 (vandetanib or motesanib or sorafenib or axitinib or gefitinib)
- #9 (targeted near6 (therap* or treatment* or intervention*))
- #10 MeSH descriptor Thrombospondins explode all trees
- #11 (anti-angiogen* near6 (drug* or agent* or therap* or treatment or intervention*))
- #12 ((VEGF or VEGF-R) near6 inhibitor*)
- #13 (angiostatin* or endostatin* or thrombospondin*)
- #14 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
- #15 #4 AND #14

Ovid MEDLINE (from January 2000 until May 2009)

1. exp Thyroid Neoplasms/
2. (thyroid adj6 (cancer or carcinom\$ or tumor?r\$ or neoplasm\$ or metast\$)).ab,ti,ot.
3. (metastatic and thyroid cancer).ab,ti.
4. or/1-3
5. exp Angiogenesis Inhibitors/
6. exp Angiostatic Proteins/
7. exp Thrombospondins/
8. ((angiogen\$ or neovasculari?ation\$) adj6 inhibitor\$).ab,ti,ot.
9. (anti-angiogen\$ adj6 (drug\$ or agent\$ or therap\$ or treatment\$ or intervention\$)).ab,ti.
10. (angiostatic adj6 protein\$).ab,ti,ot.
11. ((VEGF or VEGF-R) adj6 inhibitor\$).ab,ti,ot.
12. (tyrosin-kinase adj6 inhibitor\$).ab,ti,ot.
13. (vandetanib or motesanib or sorafenib or gefitinib or axitinib).ab,ti,ot.

Angiogenesis-inhibitors for metastatic thyroid cancer (Review)

(Continued)

14. (angiostatin\$ or endostatin\$ or thrombospondin\$).ab,ti,ot.
15. (targeted adj6 (therap\$ or treatment\$ or intervention\$)).ab,ti,ot.
16. or/5-15
17. 4 and 16
18. limit 17 to animals
19. limit 17 to humans
20. 18 not 19
21. 17 not 20

EMBASE (from January 2000 until May 2009)

1. exp Thyroid Tumor/
2. (metastatic thyroid and (tumo?r\$ or carcinom\$ or neoplasm\$ or cancer)).ab,ti.
3. 1 or 2
4. exp Angiogenesis Inhibitor/
5. exp Angiostatic protein/
6. exp Epidermal Growth Factor Receptor Kinase Inhibitor/
7. EGFR-inhibitor\$.ab,ti.
8. exp Thrombospondins/ or exp Angiostatin/ or exp Endostatin/
9. exp Vandetanib/ or exp axitinib/ or exp sorafenib/ or exp gefitinib/
10. ((angiogen\$ or neovasculari?ation\$) adj6 inhibitor\$).ab,ti.
11. (anti-angiogen\$ adj6 (drug\$ or agent\$ or therap\$ or treatment\$ or intervention\$)).ab,ti.
12. (angiostatic adj6 protein\$).ab,ti.
13. (target\$ adj6 (therap\$ or treatment\$ or intervention\$)).ab,ti.
14. ((VEGF or VEGF-R) adj6 inhibitor\$).ab,ti.
15. (tyrosin-kinase adj6 inhibitor\$).ab,ti.
16. (vandetanib or motesanib or sorafenib or gefitinib or axitinib).ab,ti.
17. (angiostatin\$ or endostatin\$ or thrombospondin\$).ab,ti.
18. or/4-17
19. 3 and 18
20. limit 19 to animal
21. limit 19 to human
22. 20 not 21
23. 19 not 22

Appendix 2. Summary of non-randomized trial results of angiogenesis inhibitors in thyroid cancer

Drug	Design of trials	Numbers of patients	Histologies included	Responses	Adverse Events
Sunitinib Cohen 2008a	Single group, phase II trial	43	37 DTC 6 MTC	DTC: 13% PR, 68% SD MTC: 83% SD	fatigue (79%), diarrhea (56%), palmar-plantar erythrodysesthesia (53%), neutropenia (49%), hypertension (42%)
Sunitinib (Ravaud 2008)	Single group, phase II trial	17	8 PTC 4 MTC 1 ATC	6.5% PR 80% SD	hypertension (41%), asthenia (41%), mucositis (29%), hand-foot syndrome (12%), thrombopenia (12%)

(Continued)

4 miscellaneous thyroid cancer

Sunitinib Goulart 2008	Single group, phase II trial	18	iodine refractory DTC and metastatic MTC	44% patients had a FDG-PET response.	neutropenia (28%), leukopenia (17%), anemia (6%), thrombocytopenia (6%), fatigue (11%), hand-foot syndrome (11%), pain (11%), gastrointestinal bleeding (11%)
Sorafenib Kloos 2009	Single group, phase II trial	56	41 PTC 25 non-PTC	for PTC: 15% PR; 56% SD longer than 6 months; median duration of PR: 7.5 months; median PFS: 15 months. no PRs were noted among non-PTC	common grade 3 adverse events included hand-foot skin reaction, musculoskeletal pain, and fatigue
Sorafenib Gupta-Abramson 2008	Single group, phase II trial	30	18 PTC 9 follicular/Hurthle cell variant thyroid cancer 1 MTC 2 poorly differentiated/anaplastic	23% PR lasting 18 to 84 weeks 53% SD lasting 14 to 89 weeks median PFS: 79 weeks	the most common events included palmar-plantar erythema, rash, fatigue, stomatitis/mucositis, weight loss, and musculo-skeletal pain
Sorafenib Ahmed 2008	Single group, phase II trial	18	10 MTC 8 DTC	10% PS 90% SD	hand foot syndrome (56%), diarrhea (50%), other skin toxicity (50%), alopecia (28%), hypertension (28%), infection (23%), nausea (17%)
Axitinib Cohen 2008b	Single group, phase II trial	60	30 PTC 15 FTC 11 Hurthle cell variant thyroid cancer 11 MTC 2 ATC 2 Others	30% PR 38% SD median PFS: 18.1 months	fatigue (50%), diarrhea (48%), nausea (33%), anorexia (30%), hypertension (28%), stomatitis (25%), weight decrease (25%), headache (22%)
Motesanib Schlumberger 2009	Single group, phase II trial	91	locally advanced or metastatic, progressive or symptomatic MTC	2% objective response 48% SD Median PFS: 48 weeks	diarrhea (41%), fatigue (41%), hypothyroidism (29%), hypertension (27%), anorexia (27%)
Motesanib Sherman 2008	Single group, phase II trial	93	progressive, locally advanced or metastatic, radioiodine-resistant DTC	14% objective response 67% SD median duration of the response: 32 weeks median PFS: 40 weeks	diarrhea (59%), hypertension (56%), fatigue (46%), weight loss (40%)

(Continued)

Gefitinib Pennell 2008	Single-group, phase II trial	27	11 PTC 6 FTC 5 ATC 4 MTC 1 Hurthle cell carcinomas	48% SD for 3 months; 24% SD for 6 months; 12% SD for 12 months; median PFS: 3.7 months median OS: 17.5 months	rash (52%), diarrhea (41%), nausea (19%), anorexia (11%)
Imatinib de Groot 2007	Single group, phase II trial	15	Metastatic MTC	27% SD over 24 months	fatigue (13%), nausea (7%), rash and malaise (13%), laryngeal swelling (13%) and hypothyroidism for patients with a history of a thyroidectomy
Thalido-mide Ain 2007	Single group, phase II trial	36	11 PTC 2 Tall-cell variant thyroid cancer 4 FTC 8 Hurthle cell thyroid cancer 4 Insular 7 MTC	18% PR 32% SD median PR duration: 4 months medial SD duration: 6 months median survival: 23.5 months for responders and 11 months for non-responders	fatigue (77%), infections (11%), pericardial effusion (3%), pulmonary embolus (3%)
Vandetanib Haddad 2008	Single group, phase II trial	19	Unresectable, measurable, locally advanced or metastatic hereditary MTC	10.5% objective response 42.1% disease control	none
Lenalidomide Ain 2008	Single group, phase II trial	25	Distantly metastatic, ¹³¹ I unresponsive (papillary, follicular, or insular) thyroid cancers	67% objective response	grade 3 toxicities were hematological: 44% neutropenia, 22% thrombocytopenia
Combretastatin A4 phosphate (CA4P) Cooney 2006	Single group, phase II trial	18	ATC	no objective response 33% SD median PFS: 7.4 weeks median survival: approximately 20 weeks	mild to moderate nausea, vomiting, headache, and tumor pain (3 patients with grade 3)

Footnotes

ATC: anaplastic thyroid cancer; DTC: differentiated thyroid cancer; FDG-PET: fludeoxyglucose positron emission tomography; FTC: follicular thyroid cancer; MTC: medullary thyroid cancer; OS: overall survival; PFS: progression free survival; PR: partial response; PTC: papillary thyroid cancer; SD: stable disease

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AIHUA TAN: protocol development

NING XIA: clinical and scientific advice, protocol development

FENG GAO: scientific advice

ZENGNAN MO: statistical advice

YUNFEI CAO: protocol development and statistical advice

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [*therapeutic use]; Neovascularization, Pathologic [*drug therapy]; Thyroid Neoplasms [*blood supply] [drug therapy]

MeSH check words

Humans