CLINICAL STUDY

Early changes in carcinoembryonic antigen but not in calcitonin levels are correlated with the progression-free survival in medullary thyroid carcinoma patients treated with cytotoxic chemotherapy

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Abstract

Introduction: The prognostic value of serum calcitonin (CT) and carcinoembryonic antigen (CEA) doubling time has been recently demonstrated in medullary thyroid carcinoma (MTC) patients. No study has yet validated the surrogate role of these markers for survival during treatment. The aim of this study was to evaluate, in patients with advanced MTC treated with cytotoxic chemotherapy, the relationship between early changes of serum CT or CEA levels and progression-free survival (PFS).

Patients and methods: The files of 28 consecutive metastatic MTC patients with progressive disease, treated with cytotoxic chemotherapy in a single tertiary referral center between 2000 and 2010, were retrospectively reviewed. Serum CT and CEA measurements and radiological Response Evaluation Criteria in Solid Tumors (RECIST) evaluations were collected every 3 months. The relationship between changes in serum CT and CEA levels at 3 months, defined by an increase or a decrease of at least 20%, and PFS according to RECIST 1.0, was estimated using Kaplan–Meier curves and log-rank test.

Results: The median follow-up for the 28 patients was 68 months. According to RECIST, a partial response, a stabilization or a progression was observed in 14, 43, and 43% of cases respectively. Median PFS from the initiation of cytotoxic chemotherapy was 4.5 months. Median PFS among patients with and without significant CT increase at 3 months was 4.6 and 3.3 months respectively ($P=0.75$). Median PFS among patients with a significant CEA increase at 3 months was 2.7 months, whereas it was 19.1 months in patients in whom CEA did not increase ($P=0.02$).

Conclusion: At 3 months, an increase of serum CEA but not of CT levels appears as a valuable surrogate marker of short PFS in MTC patients treated with cytotoxic chemotherapy. A prospective validation is expected.

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Introduction

Medullary thyroid carcinoma (MTC) is a rare cancer characterized by the production and secretion of calcitonin (CT) and carcinoembryonic antigen (CEA) into the blood (1, 2, 3). This activity has promoted numerous studies to investigate the potential role of serum CT or CEA levels as diagnostic or prognostic markers of MTC. CT is not a specific marker for MTC and is secreted in cases of C cell hyperplasia or neuroendocrine tumors (1, 4, 5, 6, 7). Nonetheless, CT is a sensitive marker for MTC and is among the highest sensitive markers in oncology (1, 8, 9, 10, 11, 12). CEA is a biomarker of several cancers and was found elevated at an advanced stage in MTC (1). After thyroid surgery,

70% of sporadic MTC patients are not cured as indicated by persistent elevated CT and CEA levels (1, 13, 14, 15, 16, 17). In these MTC patients, serum CT or CEA doubling times are correlated with overall survival and Response Evaluation Criteria in Solid Tumors (RECIST) progression (18, 19, 20) and have been proposed as a surrogate marker of overall survival (21).

Nowadays, tyrosine kinase inhibitors (TKIs), especially vandetanib, have been recommended as first-line therapy in the case of aggressive metastatic MTC patients (1) based on phase II and phase III trials in MTC patients that reported higher objective response rates compared with cytotoxic chemotherapy (22, 23). Moreover, a recently published pivotal phase III trial using vandetanib demonstrates a significant increase in

progression-free survival (PFS) in advanced MTC (24). These studies have renewed the interest of clinicians in the search for predictors or surrogates of response in MTC patients treated with TKI in order to better select patients for such therapy as well as for its maintenance. But no strict correlation between early changes in serum CT or CEA levels and tumor response has emerged yet (22, 23, 25). Only one report describes a correlation of tumor markers and response to treatment in a small series of MTC patients treated with sorafenib (25). Uncoupling impact of TKI on proliferative and secretory pathways of thyroid C cells has been suggested to explain such results (26). In this study, we speculated that cytotoxic chemotherapy could yield to different results due to a different mechanism of tumor cell-induced toxicity.

In order to further investigate the role of CT or CEA levels as surrogate markers for tumor response in MTC patients, we retrospectively reviewed files of MTC patients who were treated at the Institut Gustave-Roussy (IGR) with cytotoxic chemotherapy between January 2000 and December 2010.

Materials and methods

Patients

Approval from patients was obtained for this retrospective study. Files of consecutive MTC patients treated at the IGR undergoing cytotoxic chemotherapy for a metastatic MTC between January 2000 and December 2010 were reviewed. Inclusion criteria were: i) confirmed pathological diagnosis of MTC; ii) RECIST 1.0 progressive metastatic disease for more than 1 year at the time of treatment initiation; iii) treatment with systemic cytotoxic chemotherapy; and iv) follow-up every 3 months with serum CT and/or CEA determinations and a morphological evaluation with RECIST 1.0. Exclusion criteria were treatment with TKI drug anytime during the course of the study and changes in the methodology for CT or CEA measurements at the time of chemotherapy initiation.

Serum CT and CEA determinations

Serum CT level was measured using a MAB immunoradiometric assay (ELSA-CT; CIS Bio International, Gif-sur-Yvette, France; normal value <10 pg/ml). Intra-assay variability was <7% and inter-assay variability <12%.

Serum CEA was measured, before 2005, using a Kryptor technology with intra-assay variability <3.5% and inter-assay variability <5.5%, and after 2005 by a chemiluminescent technique (CEA Access, Beckman Coulter, CA, USA; normal value <7 ng/ml) with inter-assay variability <4%.

Serum CT and/or CEA were collected at baseline (at the time of chemotherapy initiation) and at

3 months; a decreasing level was defined as a decrease by more than 20% of its baseline value, an increasing level was defined as an increase by more than 20% and a stable level if it ranged between -20 and $+20\%$ of its basal level.

Imaging and RECIST criteria

All patients had a morphological evaluation at baseline and every 3 months during chemotherapy consisting of neck, chest, and abdomen computed tomography scan, liver magnetic resonance imaging (MRI), bone scan and spine MRI when considered appropriate. Tumor response was evaluated as RECIST 1.0 every 3 months after initiation of chemotherapy and was compared with baseline results. According to RECIST, results were classified as partial response (PR) if the sum of the target lesion diameters decreased by more than 30%, as progressive disease (PD) if it exceeded 20% and as stabilization if it was in between (27). In patients with bone metastases only, appearance of a new bone metastasis confirmed by conventional imaging was classified as a progression. In addition, death from any cause was classified as PD. Three patients had bone metastases only, and were followed with bone scan and MRI.

Chemotherapy

Various protocols were used as first-line chemotherapy. Nine patients received 5-fluorouracil (5FU) with dacarbazine or temozolomide, five patients received 5FU with streptozocin and eight patients received an alternative regimen of 5FU–dacarbazine and 5FU (replaced by doxorubicin in five cases)–streptozocin as described in the literature (28). The remaining six patients were treated by other types of chemotherapy such as gemcitabine, cisplatin combined or not with etoposide, FU, and irinotecan or carboplatin. The median number of cycles was 4.5 (range: 2–12).

Statistical analysis

Quantitative data were expressed as mean and s.d. and qualitative data were expressed as percentage. PFS was defined as the time between chemotherapy initiation and the first subsequent event (progression or death from any cause). Patients who were alive and who did not progress were censored at the date of their last follow-up visit. PFS was estimated by Kaplan–Meier method. Early changes in serum CT or CEA levels at 3 months and their relationship with PFS were analyzed using the log-rank test. Results were classified as concordant, in case PR, stabilization, or PD on imaging were consistent with serum CT and CEA decreased, stable, or increased levels respectively. Otherwise, results were classified as discordant. Major discordance was defined by CT or CEA decrease or increase in case of

PD or PR respectively. All reported *P* values are two sided and the significance level was 0.05. Analyses were performed using SAS Statistical Software version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Clinical characteristics of patients and initial treatment

Records of 40 consecutive MTC patients were reviewed (Table 1). Seven patients received a TKI therapy as second- or third-line treatment and five patients did not have a biological or morphological evaluation at 3 months. Overall, 28 patients met the inclusion criteria and formed the basis of this report.

The clinical characteristics of the 28 patients are reported in Table 1. There were 19 males and nine females, aged between 22 and 75 years with a median age of 58 years. Germinal RET mutation was found in five (18%) patients. All patients were initially treated by total thyroidectomy and cervical lymph node dissection. The median time from diagnosis to first distant metastasis was 2 years (range: 0–8 years) and the

Table 1 Clinical characteristics of patients.

	n=28 patients
Sex	
Male	19
Female	9
Median age (years; range)	58 (22–75)
Stage of tumor at diagnosis	
I	0
II	1 (4%)
III	6 (21%)
IV	17 (61%)
Unknown	4 (14%)
Median time from diagnosis to first metastasis (years)	2
Germline RET mutation	
Present	5 (18%)
Absent	14 (50%)
Unknown	9 (32%)
Median time to chemotherapy since initial diagnosis (years)	2
Mean/median calcitonin value (range) before chemotherapy (pg/ml)	32 784/2221 (33–328 000)
Mean/median CEA value (range) before chemotherapy (ng/ml)	419/83 (3–3428)
Tumor metastatic organs	
Lungs	14
Liver	13
Bone	17
Choroid	1
Brain	1
Kidney	1
RECIST 1.0: PR or stabilization	
5FU + dacarbazine (nine patients)	6
5FU + streptozocin (five patients)	4
5FU + dacarbazine alternating with adriamycin + streptozocin (eight patients)	4
Others (six patients)	2

Figure 1 Early changes in calcitonin levels and tumor response (RECIST) at 3 months.

median time from diagnosis to first chemotherapy treatment was also 2 years (range: 0–11 years). Fourteen patients (50%) received external radiation therapy to the neck and mediastinum. All patients had metastatic disease with documented progression by imaging over 1 year or less at the time of chemotherapy initiation. The most frequent site of metastases was bones, followed by lungs and liver.

Results of chemotherapy: RECIST 1.0 evaluation and survival

At 3 months, a PR was observed in four patients (14%), stabilization in 12 patients (43%), and PD in 12 patients (43%). Median PFS and overall survival (OS) were respectively 4.5 months and 2.5 years. Thirteen patients were controlled for more than 6 months: ten of them were treated with 5FU–dacarbazine combined or not with 5FU–streptozocin, and two received 5FU–streptozocin alone. Overall survival at 1 and 5 years were 60% (95% CI=42–75) and 15% (95% CI=5–39) respectively.

Early changes in serum CT and CEA levels and tumor response (RECIST) at 3 months

Early changes in CT levels were evaluable in the 28 patients and concordant with RECIST results in 15 (54%) cases (Figs 1 and 2). The following discordant variations of CT were observed in 13 patients (46%): increased CT levels in patients with PR (two cases), decreased CT levels in patients with PD (two cases), and increased or decreased CT levels in patients with stable

Figure 2 Early changes in CEA levels and tumor response (RECIST) at 3 months.

disease (four and five cases respectively). Major discordance was therefore found in four cases (14%).

Early changes of serum CEA levels were evaluable in 25 patients and concordant with RECIST results in 19 (76%) cases. The following discordant changes of CEA were observed in six patients (24%): increased or decreased CEA levels in patients with stable disease (one and five cases respectively). No major discordance was found.

Median PFS as function of early CT or CEA changes

Median PFS was 4.6 months when CT level was stable or decreasing, and 3.3 months when CT level increased; there was no statistical difference between the two groups ($P=0.75$; Figs 3 and 4).

Median PFS was 19.1 months when CEA level was stable or decreasing, and 2.8 months when CEA level increased; the difference being statistically significant between the two groups ($P=0.02$).

When a threshold of early CT or CEA change of 50% was considered, the results were not modified. Furthermore, no correlation between early CT or CEA changes and overall survival was found.

Discussion

In this study, CEA and CT markers are investigated as surrogates of cell cytotoxicity induced by traditional DNA damage by cytotoxic agents, which modalities of cell cytotoxicity differ from those of the TKIs.

Our study suggests for the first time that in MTC patients treated with cytotoxic chemotherapy, early changes in serum CEA levels at 3 months could be considered as surrogate marker of PFS. Indeed, an increase in CEA level during the first 3 months of chemotherapy was associated with a significantly shorter PFS ($P=0.02$), and this should lead to discontinuation of cytotoxic chemotherapy. In contrast, the 19.1-month PFS observed in CEA responders validates the use of cytotoxic chemotherapy in these selected patients. No significant relationship was observed between changes in CT levels during the first 3 months of chemotherapy and tumor response or PFS. In the absence of validated predictors of response to cytotoxic chemotherapy in MTC patients, early determination of CEA appears as a useful tool to decide whether to maintain chemotherapy or not. In addition, in the absence of complete remission observed in patients treated by TKI, cytotoxic chemotherapy will probably play a role in the treatment of MTC patients as either post first- or second-line therapy or in future protocols analyzing the impact of drug combinations. In this regard, historical cytotoxic chemotherapies used in neuroendocrine tumors, such as 5FU–dacarbazine, appear the best option.

A surrogate marker can be defined by any biological measurement that is used in therapeutic trials as a substitute for a clinically meaningful endpoint and is expected to predict the effect of the therapy early (29, 30). It is used at the initiation of a given treatment to predict tumor response early in a patient to avoid undue toxicity. Recently, CT or CEA doubling time was recommended by ATA guidelines (1) as a marker of progression calculated by using a minimum of four CT values preferably over a 2-year period. Such recommendations cannot be applied to surrogate markers since the shortest delay of information is required to consider a biomarker as a valuable surrogate. Interestingly, in this study, two measurements at 3 months' interval

Figure 3 PFS according to changes in calcitonin (CT) levels at 3 months after initiation of cytotoxic chemotherapy.

Figure 4 PFS according to changes in CEA levels at 3 months after initiation of cytotoxic chemotherapy.

were found sufficient to predict PFS with CEA measurements. We speculate that treatment intervention in the case of cytotoxic chemotherapy improves the predictability of CEA measurement.

The higher concordance found between CEA and RECIST results compared with CT measurements could not only be related to the high day-to-day variability of CT results but also to a greater influence of drug interference and levels of urea and creatinine (31, 32, 33), to the rapid degradation of CT after blood sampling, or to the hook effect in the case of very high levels of CT achieved in metastatic MTC patients (31, 34). Surprisingly, no clear correlation has yet been reported between early changes in CT or CEA levels and response to TKI (22, 23, 26). Because RET kinase mediates a physiologic pathway controlling CT secretion, it was expected that RET kinase inhibitors could affect both the secretory activity and the growth of the neoplastic C cells (26). However, no strict correlation was observed (35) and even paradoxical increase in biomarkers was observed in responders (23, 36, 37). These results suggest that the mechanisms leading to tumor control and marker secretion are dissociated in the setting of TKI administration. In contrast, the present study suggests more straightforward relationship between CEA secretion and tumor control in patients treated with cytotoxic chemotherapy.

Conclusion

Our study demonstrates that early change in CEA levels at 3 months is a surrogate marker for PFS in advanced MTC treated with cytotoxic chemotherapy. In case of CEA progression at 3 months, discontinuation of cytotoxic chemotherapy should be discussed. A prospective validation is expected to confirm these results.

Declaration of interest

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

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Author contribution statement

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