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Phase II study of etoposide (VP-16) in patients with thyroid cancer with no prior chemotherapy: an Eastern Cooperative Oncology Group Study (E1385)

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This study of etoposide in thyroid cancer was designed to determine the activity and toxicity of etoposide in a variety of inoperable, thyroid hormone insensitive, and radio-iodine resistant primary cancers of the thyroid. The patients were required to have an ECOG performance status of at least 3 and no previous exposure to chemotherapy. The etoposide was given at a dose of 140 mg/m^2 daily for 3 days and every 3 weeks until progression. The study was closed after 18 months because of poor accrual. There were no responses seen among the 10 patients accrued. The toxicity was primarily hematologic. There was no evidence of activity of etoposide in thyroid carcinoma, although this study lacked significant power because of the poor accrual.
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Introduction

Thyroid cancers are the most common type of endocrine malignancy accounting for 17 200[1] cases per year, and accounting for 1120 deaths per year. Histologically these tumors are categorized as well-differentiated (papillary, follicular, mixed papillary and follicular, and Hurthle cell carcinomas), medullary carcinomas (MTC), and anaplastic carcinomas. Surgery is the mainstay of treatment for the well-differentiated tumors and MTC. Well-differentiated tumors are treated with radioactive iodine post-operatively and in the setting of metastatic disease. Attempts at treatment with chemotherapy have proven to be disappointing.

Agents known to be active against thyroid cancer include doxorubicin and cis-platinum. A study comparing doxorubicin at 60 mg/m^2 to the same dose of doxorubicin with cis-platinum at 40mg/m^2 revealed response rates of 17% and 26% respectively, but there were 5 complete responses on the combination therapy arm and none with the single agent.[2] Another study showed some improvement in symptom control with single agent therapy using etoposide, cis-platinum and carboplatin.[3]

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There have been a small number of cases in which etoposide has been evaluated in thyroid cancer. A report of four patients with thyroid carcinoma (1 anaplastic, 2 medullary and 1 differentiated tumor) treated at Roswell Park Cancer Center noted partial responses in the anaplastic and one of the medullary tumors.[4] There was also another report of a partial response by the EORTC.[5] Another study examined the role of combination chemotherapy in patients with metastatic nonanaplastic thyroid cancer using combinations of etoposide with doxorubicin, 5-fluorouracil and cyclophosphamide. No responses were seen, but the dose of etoposide used was very low.[6] Interestingly the thyroid has been shown to have high etoposide concentrations several days after administration of the drug.[7]

Etoposide was felt to be a promising drug to explore in this relatively resistant tumor because of the substantial activity documented in a broad spectrum of other tumors and the suggestion of its activity in thyroid cancer in the few case reports noted. This study of etoposide in thyroid cancer was made by the Eastern Cooperative Oncology Group from July 1986 to January 1988 and was designed to determine the activity and toxicity of etoposide in a variety of primary cancers of the thyroid.

Patients and methods

Eligibility

Patients were required to have histologically confirmed thyroid carcinoma consisting of one of the following types: differentiated carcinoma (including variants of papillary and/or follicular carcinoma), medullary carcinoma, and anaplastic carcinoma (including spindle and giant cell carcinoma, sarcoma, and squamous cell carcinoma). Patients with differentiated carcinomas were required to exhibit evidence of progression of disease with radio-iodine treatment and continuous suppressive thyroid hormone therapy. Patients were required to have inoperable, measurable disease and an ECOG performance status of 3 or less. Patients with exposure to previous chemotherapy were excluded. Adequate bone marrow function (WBC $>4000/mm^3$ and platelet count $>100\,000/mm^3$), renal function (creatinine <1.5 mg/dl, BUN <25 mg/dl, creatinine clearance >60 ml/min) and hepatic function (bilirubin <1.5 mg/dl and SGOT <60 IU/ml) were required. All patients were required to give written informed consent.

Stratification factors

Patients were stratified upon randomization according to histology (differentiated, medullary or anaplastic), metastatic site (lymph node only, visceral with or without nodal involvement, and bone involvement with or without visceral or nodal involvement) and performance status ($0-1$ *vs* $2-3$).

Response Definitions

Patients were required to have bidimensionally measurable disease. A complete response was defined as disappearance of all evidence of disease clinically, radiologically and by laboratory testing for more than 1 month.

A partial response was defined as a decrease by 50% or more in the sum of the cross-sectional areas of all measurable lesions for more than 1 month, in the absence of increase in the cross-sectional area of an individual lesion by more than 25% or the appearance of any new lesion.

Progression of disease was defined as increase in the cross-sectional area of any measurable lesion by 25% or more, or the appearance of new lesions.

Stable disease was defined as there being neither a response nor a progression of disease.

Pre-treatment and follow-up evaluation

All patients underwent full physical examination and evaluation of tumor size and laboratory evaluation consisting of complete blood counts, serum electrolytes, and liver function tests upon entry to the study and prior to each course of chemotherapy. Electrocardiogram and chest X-rays and thyroid function tests were done every other cycle. Thyrocalcitonin levels were drawn prior to every cycle in patients with medullary carcinomas.

Treatment plan

Etoposide was administered at a dose of $140\,mg/m^2$ daily for 3 days every 3 weeks. At least two cycles of therapy were to be administered to evaluate response unless marked progression was obvious.

Suppressive therapy with thyroid hormone and monitoring of the TSH was to be done during protocol therapy.

Dose modification

The dose of etoposide was to be adjusted for hematologic toxicity as follows: 50% of the dose was to be given if the WBC was between 2000 and 4000/mm^3 or the platelet count was between 50 000 and 100 000mm^3. If the platelet count was less than 50 000/mm^3 or the WBC was less than 2000/mm^3 the chemotherapy was held until recovery of counts.

The does of etoposide was reduced by 50% if the creatinine was between 1.5 and 2.0 mg/dl or the creatinine clearance was between 40–60 ml/min. The dose was held if the creatinine was greater than 2.1 mg/dl or the creatinine clearance was less than 40 ml/min.

Statistical design and analysis

The study planned to accrue 20 evaluable patients and etoposide was to be considered active if five or more responses were noted. If etoposide had a true 30% response rate then there would be a 76% chance of seeing this many responses; if it had a true 10% response rate, there would be only a 4% chance of seeing this many responses.

Results

Only 10 patients were registered. The study was closed after 18 months because of poor accrual.

Patient characteristics

The median age was 65.5 y, with a range of 40–76 y. Four were female, 6 were male. Five patients had visceral disease only; 5 had bone disease with or without visceral disease.

Only 5 of the 10 patients' pathologies were reviewed by the Pathology Review Committee (see Table 1). Two of the cases that were entered by institutions as having anaplastic histologies were found to have only differentiated histologies (poorly differentiated follicular and pure Hurthle cell carcinoma). As patients with differentiated carcinoma were required to be refractory to radioiodine therapy, these cases did not meet eligibility criteria. One of these two cases also did not receive continuous thyroid suppressive therapy as required. One case of a Hurthle cell carcinoma (with slides not reviewed by the Pathology Review Committee) also did not receive radioiodine therapy as required by eligibility criteria and is also considered ineligible. Two cases were submitted as primary squamous cell carcinomas of the thyroid, but were felt by the pathology review committee to be more consistent with metastatic disease to the thyroid.

Response

No patient had a response. An exact one-sided 90% confidence interval for the response rate is 0% to 20.6%. Thus the observed data are consistent with a true probability of response of < 0.206 with 90% confidence.

The median survival was 9.9 months with a range from 0.4 months to 45 months (Figure 1). The three cases with the longest survival (29.0, 29.1 and 45 months) all had differentiated tumors. Failure-free

Table 1 Treatment summary

Instit path	*Path review*	*Number of cycles*	*Response*	*Time to Progression (months)*	*Survival (months)*
Anaplastic	Poorly diff. follicular	2	Prog	1.1	10
Papillary/follicular	Diff. papillary	3	Prog	2.5	9.9
Squamous	Squamous	1	Uneval	0.5	1.4
Anaplastic/Hurthle	Hurthle cell	2	Prog	1.2	10
Anaplastic/11squamous	Squamous	1	NC	–	0.4
Medullary	–	3	Prog	2.2	8
Hurthle	–	1	Uneval	2.6	29.1
Medullary	–	2	Prog	1.2	8.1
Papillary/follicular	–	14	Prog	10.2	45
Follicular/Hurthle	–	3	Prog	1.4	29

NC = no change; Prog = progression; Uneval = unevaluable.

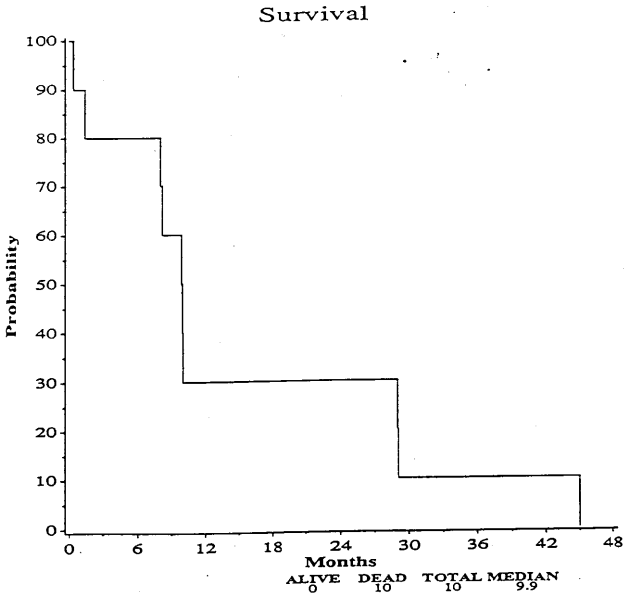

Figure 1 *Survival.*

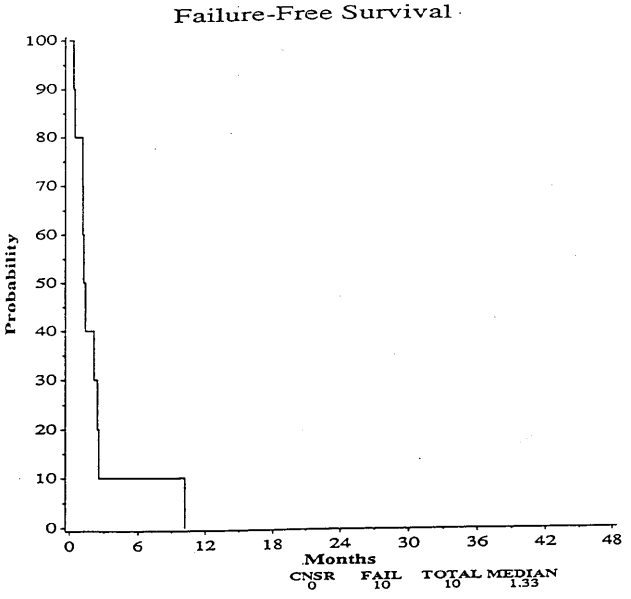

Figure 2 *Failure-free survival.*

survival (FFS) is shown in Figure 2. The median FFS was 1.3 months. One patient died of toxicity and did not have documented progression before death.

Toxicity

The toxicities were primarily hematologic. There were two grade 4 (life-threatening) cases and one lethal case of leukopenia. There was one case of a grade 3 (severe) respiratory complication. There were no other grade 3 or 4 toxicities.

Discussion

There was no evidence of response to etoposide in the cases of thyroid cancer on the study. The study, however, lacked significant power given the difficulty in obtaining adequate accrual. The three patients with differentiated tumors who did not receive a trial of radioiodine therapy and are, therefore, not known to be refractory to it are probably better-risk patients than called for in the eligibility section. Thus, including them in the analysis probably confers an optimistic bias.

Several cases had long survivals of more than 2–3 years despite lack of measurable response to etoposide. These cases all had differentiated histologies and their long survival is likely related more to underlying natural history of the disease than any specific effect of the chemotherapy.

The study accepted different types of thyroid histologies, all of which may have unique patterns of response to etoposide. Medullary carcinoma of the thyroid may, for example, share more similarities with other neuroendocrine tumors than with other thyroid tumors. Neuroendocrine tumors such as oat cell tumors of the lung are known to be very responsive to etoposide and there is some suggestion that APUD tumors including medullary carcinoma of the thyroid may be responsive to etoposide.[3,8]

Given the relative rarity of thyroid tumors, more cooperative group studies with newer drugs are needed to help develop definitive guidelines for treatment. Combined chemotherapy–radiation protocols might be considered for the very aggressive anaplastic tumors which are rapidly growing and exert their effects locally. Perhaps further studies involving medullary carcinoma of the thyroid should be included in studies of other neuroendocrine tumors.

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