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Case Report

Case Report: Vigil Therapy in Pathology Defined High-Risk Differentiated Thyroid Cancer Compounded by Post Ablation High-Risk Factors

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Abstract

Thyroglobulin levels ≥50 µg/L following thyroidectomy and I131 ablation correlate with poor prognosis in patients with high risk Differentiated Thyroid Cancer (DTC). We describe a case of a 54 year old woman with differentiated thyroid cancer and high thyroglobulin up to 220 µg/L following thyroidectomy and I131 ablation who demonstrated marked response to a novel immunotherapy involving autologous tumor cell transfected with a GMCSF/bi-shRNA furin expressive plasmid (Vigil). Activity is highlighted by four year disease free survival in correlation with immune activation as measured by ELISPOT assay of peripheral blood mononuclear cell reaction to autologous tumor. Further investigation with Vigil in differentiated thyroid cancer is warranted.

Introduction

In a recent analysis of 243 patients with high-risk Differentiated Thyroid Cancer (DTC) [1] following thyroidectomy and I131 ablation, thyroglobulin (Tg) levels ≥50 µg/L within 2 years of diagnosis were shown to be a significant predictor for disease persistence with a 97% Positive Predictive Value (PPV) as well as for Progression Free Survival (PFS) [2]. We describe a high-risk DTC patient who, following thyroidectomy and I131ablation, demonstrated persistent Tg > 50 µg/L with no evidence of residual disease by radionuclide scan, CT or regional ultrasound. In view of this incomplete biochemical response, the patient underwent treatment with a novel immune modulating therapy called Vigil [3-7]. Vigil elicited a serological immune response and was followed by stabilization of Tg expression. This patient remains alive with neither visible disease nor evidence of structural or biochemical progression 4 years after treatment initiation.

Case Report

Patient #075 was a 54-year-old asymptomatic woman when, in 2013, she was found to have nodular enlargement of her thyroid gland on routine physical examination. An ultrasound revealed a mass in the left lobe with multiple adjacent enlarged lymph nodes. On 05/11/2013 biopsy showed malignant papillary thyroid carcinoma. She underwent a total thyroidectomy with node dissection. Final pathology revealed a 4 cm papillary carcinoma, follicular variant, replacing the left lobe with metastases to six of seven left regional nodes. Lympho vascular invasion and tumor capsular penetration were present as well as perineural and extra thyroidal extension. Therefore, the tumor was staged IVA (T4N1b) and deemed high risk per the American Thyroid Associated (ATA) Risk Stratification System [8]. She underwent ablative I131 therapy (160 mCi) on 7/31/2013. A head and neck sonogram on 10/30/2013 showed no residual thyroid tissue, however the Tg concentration was 220 µg/L with thyroglobulin antibody < 20 IU/mL (Figure 1). Following thyrogen stimulation she received a second I131injection (4.9 mCi) followed by a diagnostic scan on 3/21/2014, which showed no evidence of residual disease. A follow up sonogram confirmed no evidence of loco-regional disease, however her thyroglobulin remained elevated at 77.5 µg/L. Distant metastases were further excluded by CT scan of neck through pelvis. Thyroid hormone therapy was started with TSH stabilization within normal levels. On the basis of the risk attendant to the persistently elevated thyroglobulin following debulking surgery and I131 therapy, Patient #075 elected to participate in a MCCRC phase I study assessing low dose Vigil (1x10^6 cells/inj) [9].

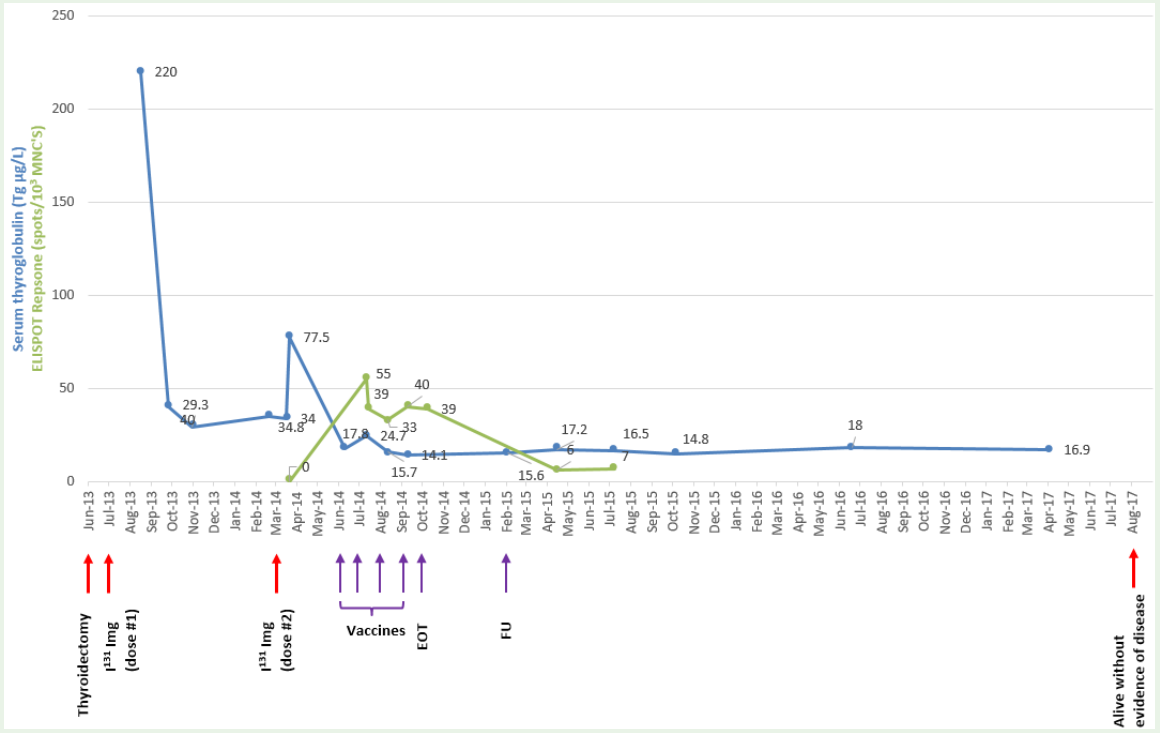

Figure 1: Correlation of Thyroglobulin Level and ELISPOT Response of Patient #075, a 54 year Female with Stage IV Malignant Papillary Thyroid Cancer Following Surgery/I131 Failure x2 (Time Course of Therapy is Also Shown below Time Line).

The first Vigil dose was administered on 6/16/2014. The immune response was measured by IFN-γ ELISPOT assay at baseline before initiation of Vigil and prior to each of the subsequent treatments (Figure 1). All 4 cycles of Vigil were well tolerated without Grade 3 or higher adverse events. The post diagnostic 4.9 mCi 131I scan thyroglobulin of 77.5 µg/L decreased to 17.8 just prior to Vigil and continues to remain stable (range, 14.1-18 µg/L), the most recent being 16.9 µg/L (Figure 1). A positive ELISPOT response (>10 spots/10^5 MNC's) was observed within 1 month of Vigil start, persisted at 5 months after the first dose of Vigil but decreased to 6 and 7 spots/10^5 MNC's at 7 months. Unfortunately, there is not an adequate amount of non-transfected tumor tissue available to continue further ELISPOT testing. There is still no evidence of disease on follow up CT scans. The patient is now > 4 years from diagnosis.

Discussion

This is a case of a high-risk DTC patient based on surgical and pathological findings elevated to a higher risk status based on an incomplete biochemical response following disease specific therapy. Further, the follicular variant of papillary carcinoma is associated with a significantly higher risk of disease-specific mortality compared to classical papillary carcinoma [10]. The role that Vigil, an autologous tumor/GMCSF-bi-shRNA furin DNA transfected immunotherapy, may be playing in her continued state of well-being with neither overt disease recurrence nor continued rise in Tg levels is suggested by the elicited immune response as measured by IFN-γ ELISPOT assay. That this functional assay correlates with survival and time to progression has been shown in a broad range of solid tumors as reported in prior publications [3-7]. Moreover, correlation of immune response induction and clinical benefit has been observed with low dose Vigil (<1x10^7 cells/inj for minimum of 4 injections) [9]. Further experimental trial testing of Vigil and immune responsiveness of DTC is recommended.

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Disclosure/Conflict of Interest

The following authors are shareholders in Gradalis, Inc. and Strike Bio: Donald D. Rao, Neil Senzer and John Nemunaitis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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