Case Reports on Cancer Patients Using Anvirzel®, a Defined Extract of *Nerium Oleander*

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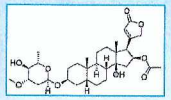
Introduction

Anvirzel, an extract of *Nerium oleander*, is currently in Phase I clinical trials in cancer patients. It's major active compound, oleandrin, is a cardiac glycoside that binds to the Na,K-ATPase enzyme alpha-3 subunit on cells, causing the subunit to translocate from the cell membrane to the perinuclear region. Historically, cardiac glycosides have been utilized in the treatment of congestive heart failure; however, exposure of the alpha-3 subunit to certain cardiac glycosides also results in anticancer activity. Oleandrin thus selectively targets human malignant cells, resulting in in cell cycle arrest, autophagic cell death, and apoptosis.[1]



In excessive doses, *Nerium oleander* has been associated with nausea, vomiting, progressing to atrioventricular blocks, arrhythmias and premature ventricular beats. However, while oleander exposures are commonly reported to Poison Control Centers, there has only been 1 US death between 1983-2011, and that was linked to suicide from an extreme dose.[2] Based on Phase 1 testing, 1.2 mL/m^2/day intramuscular injections of Anvirzel extract can be safely tolerated. The only associated toxicities observed included injection site reactions, fatigue, nausea and dyspnea.[3] A sublingual dose of 10.2 mg/day can also be safely tolerated.

Anvirzel has been supplied to some patients through personal use exemptions. The present study discusses patient cases to further assess Anvirzel for toxicities, interactions with chemotherapy, as well as the drug's effects on patient outcomes.

Methods

With appropriate patient consent, medical records were assessed for the following data: 1) Diagnosis and course of disease 2) Use of chemotherapy combined with Anvirzel 3) Evidence of toxicity possibly related to Anvirzel 4) Anvirzel and chemotherapy-related toxicities based on Common Toxicity Criteria for Adverse Events (CTCAE).

Results

Table 1 presents the demographics of the 9 patient cases that were assembled, 6 of whom were also treated with integrative therapies (diet, exercise, supplements) at the Block Center for Integrative Cancer Treatment. All but 1 were stage IV cancer patients.

Table 1: Patient Demographics

Pt #, sex	Cancer site, stage	Metastatic sites	Duration of Anvirzel treatment	Survival from diagnosis (Typical Survival)
1, m	Colon, IIIB	Lymph nodes	3 y, 2 m	5 y, 11 m (46.5% 5-year)
2, f	Colon, IV	Liver, lung	2 y, 8 m	6 y, 11 m (5.7% 5-year)
3, f	Colon, IV	Liver	17 m	4 y, 8 m (5.7% 5-year)
4, m	Rectal, recurrent	Lung	11m	5 y, 0 m (6.0% 5-year)
5, f	Renal cell, recurrent	Lung	5 y, 4 m	5 y, 11 m (8.2% 5-year)
6, m	Pancreatic neuro-endocrine, IV	Liver	11 y, 6 m	11 y, 0 m (20% 8-year)
7, f	Pancreatic adenocarcinoma, recurrent	Lung	3 y, 2 m	4 y, 8 m (2.8% 5-year)
8, f	Pancreatic adenocarcinoma IV	Colon, ovary, carcinomatosis	5 y	5y, 1 m (2.8% 5-year)
9, m	NSCLC, IV	Liver, adrenal, bone	2 y, 1 m	2 y, 8 m (11% 3-year)

Results

Survival times of patients on Anvirzel are shown in Table 1. Most patients exceeded typical survival times for disease and stage. Additionally, several patients demonstrated disease stability and tumor regression for extended periods while solely on Anvirzel, or while receiving palliative therapy (Table 2).

Table 2: Observed disease stability and tumor regression

Pt #	Disease Stability	Tumor Regression
1 Colon, IIIB	10 months (Anvirzel + integrative program)	
5 Renal Cell, recurrent		Tumor regression over 12 months (no chemotherapy)
6 Pancreatic neuro-endocrine, IV	8 years (Anvirzel + 8 cycles of one chemotherapy regimen)	
7 Pancreatic adenocarcinoma, recurrent	15 months (Anvirzel + integrative program-no chemotherapy)	
8 Pancreatic adenocarcinoma, IV	20 months (Anvirzel + 5th line Mitomycin-C)	

Extended periods of concurrent Anvirzel administration with conventional chemotherapy did not result in additional dose-limiting toxicities. The majority of adverse effects experienced by patients were considered CTCAE Grade 1 or 2 and associated with the chemotherapy regimen. The two incidences of grade 1 toxicities linked to Anvirzel included mild tingling, numbness, burning sensation in mouth and mild dizziness and lightheadedness (Table 3).

Results

Table 3: Toxicities associated with chemotherapy taken concurrently with Anvirzel

Pt #	Regimen	Grade 1 toxicities	Grade 2 toxicities	Grade 3 toxicities	Anvirzel toxicity
1	5FU/leucovorin/bevacizumab	✓	✓	✓	
2	FOLFIRI/bevaci-zumab (7th line)	✓ (Anvirzel)	✓		Mild tingling, numbness, burning sensation in mouth
3	5FU/leucovorin/bevacizumab	✓	✓		
4	FOLFIRI/bevaci-zumab	✓	✓		
9	Carboplatin/pac-litaxel	✓ (Anvirzel)	✓		Mild dizziness, lightheadedness
	Pemetrexed/ bevacizumab	✓		✓	

Conclusion

In all 9 cases, patients received Anvirzel for extended periods of time with and without multiple cycles of chemotherapy. The associated toxicities were those typical of chemotherapy, while only two Grade 1 toxicities were linked to Anvirzel. Of the 9 patients, 1 experienced disease regression with Anvirzel monotherapy, while 4 other patients experienced disease stability for extended times. In addition, all of the patients exceeded the average survival times for their diagnosis. Based on the demonstrated safety and improved outcomes associated with Anvirzel, further clinical research is warranted.

References

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3. Mekhail T et al. Invest New Drugs 2006; 24:423-7

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