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Case Report

Marine-Derived Therapeutics for the Management of Glioblastoma: A Case Series and Comprehensive Review of the Literature

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Simple Summary: Glioblastoma is a fatal brain tumor, with recurrence and eventual mortality inevitable despite the current standard of care treatments. The identification of novel therapies capable of extending survival is therefore imperative. In this case series, we describe two cases in which marine nutraceuticals were used in the management of glioblastoma and conferred a survival benefit exceeding the currently recognized median survival time of standard of care treatment. In the subsequent literature review, we describe the mechanisms underlying the anticancer and immunogenic properties of marine nutraceuticals, which may contribute to their demonstrated therapeutic benefit.

Abstract: Introduction: Glioblastoma is a fatal intracranial neoplasm that is refractory to treatment, with inevitable disease recurrence and progression to death. Marine-derived compounds, including those found in nutraceutical products, may provide therapeutic benefit in the setting of glioblastoma. We present two patient cases whose courses demonstrate a compelling role for marine-derived products in the management of glioblastoma. Cases: Case 1 describes a patient with *MGMT* promoter unmethylated glioblastoma who went on to complete standard of care chemoradiation along with concurrent use of a majority sea cucumber (MSC) blend known as SeaCare® (SeaCare, Torrington, CT, USA). Her survival of over 2 years significantly exceeds the recognized median survival time of glioblastoma. Case 2 describes a patient with a complicated course who experienced dramatic improvement after the initiation of the MSC blend, with an exceptional survival time of over 4 years post-diagnosis. Discussion: The mechanisms of marine-derived products that underlie these dramatic clinical effects are likely multifaceted but may hinge on the modification of the tumor immune microenvironment and suppression of tumorigenic effects. Specifically, the change in tumor-associated macrophages (TAMs) within the tumor microenvironment is central to this complex interplay. Conclusions: Ultimately, the use of marine products in the treatment of glioblastoma may present a novel and promising therapeutic strategy that warrants further investigation.

Keywords: glioblastoma; microenvironment; tumor-associated macrophage; marine derived; sea cucumber; seagrass; sea urchin; sea squirt

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1. Introduction

Glioblastoma is a complex, deadly, and treatment-resistant neoplasm. The median overall survival is 14.6 months, with progression common within the first 2 years of diagnosis. The current standard of care consists of maximal safe resection or biopsy, followed by concomitant radiation therapy with temozolomide (TMZ), followed by maintenance TMZ for 6 to 12 months with or without the addition of tumor-treating fields [1]. Prognosis is improved in patients who undergo gross total resection and whose tumors demonstrate *O6-methylguanine-DNA methyltransferase* (*MGMT*) promoter methylation. In those patients with

MGMT promoter hypomethylation, the outcomes are notably worse. Standard therapies for recurrent disease remain limited [1].

Meanwhile, nutraceutical marine compounds continue to be an emerging area of interest in the treatment of cancers, demonstrating potent therapeutic effects against a wide range of cancers [2], with some compounds going on to demonstrate significant efficacy in human clinical trials. SeaCare® is a proprietary nutraceutical blend consisting of a majority of sea cucumber (MSC) blend with smaller fractions of seagrass, sea squirt, and sea urchin. It is currently commercially available as a nutraceutical dietary supplement.

In this case series, we describe two patients with newly diagnosed glioblastoma who self-reported taking an MSC blend either while on active chemoradiotherapy or after the completion of maintenance TMZ, respectively. This manuscript will also go on to discuss the hypothesized mechanisms of action for marine-derived agents, specifically focusing on the tumor immune microenvironment as well as other proposed anticancer properties.

2. Case Series

2.1. Patient 1

A 74-year-old female, with a past medical history of chronic obstructive pulmonary disease, Charcot–Marie–Tooth disorder, abdominal aortic aneurysm status post repair, hypertension, and hyperlipidemia, presented with a seizure-like event in July 2020. Magnetic resonance imaging (MRI) with gadolinium revealed a 2.0 × 2.7 cm right parietal contrast-enhancing mass. Shortly after neuroimaging, the patient underwent a craniotomy. Postoperative imaging was suggestive of a gross total resection with postoperative blood products within the cavity. Pathologic diagnosis revealed a glioblastoma with wild-type *isocitrate dehydrogenase 1* (*IDH1*) and an unmethylated *methylguanine methyltransferase* (*MGMT*) promoter region.

Two weeks following the craniotomy, the patient self-initiated the MSC blend, dosed at 40 mL twice daily. This is double the amount recommended by the manufacturer. Approximately a month after her craniotomy, she initiated concurrent chemotherapy and radiation. She went on to complete a full course of chemoradiation with a total dose of 6000 cGy delivered over 6 weeks concurrent with temozolomide (TMZ) and an MSC blend. Following the completion of chemoradiation, she opted not to undergo maintenance TMZ but continued the MSC blend as described previously. The patient remained compliant with this regimen and continued with routine surveillance MRI scans [Figure 1] and medical follow-up. As of the composition of this manuscript, she remains alive and clinically well over 3 years and 5 months following her diagnosis.

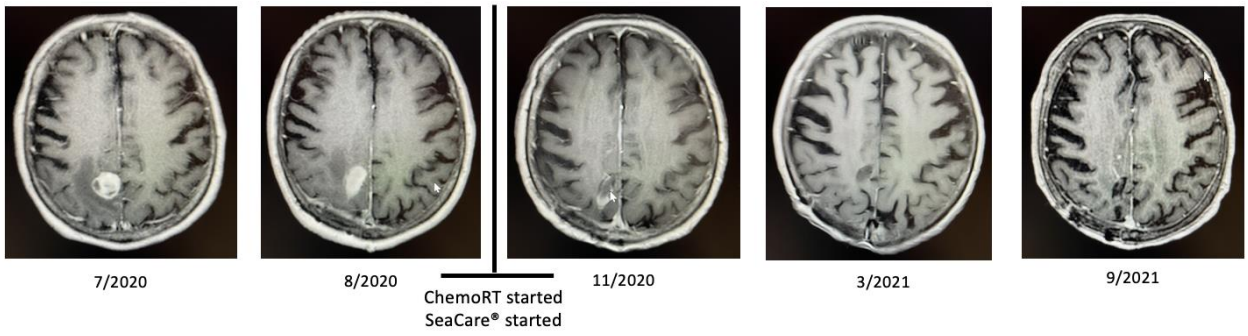

Figure 1. Serial radiographic response of Patient 1. Gadolinium-enhanced MRI shows a significant decrease in tumor size after a 6-week course of concurrent chemoradiation and the initiation of marine nutraceutical products. Even in the absence of adjuvant temozolomide, she achieved a durable response on maintenance marine nutraceuticals alone.

2.2. Patient 2

A 41-year-old female presented with headaches and gait instability in September 2018. MRI of the brain with gadolinium revealed a 3.5 × 3.0 cm left frontal, intraventricular mass

crossing the corpus callosum. Biopsy and pathology analysis confirmed a diagnosis of glioblastoma that was *IDH1* wild-type, and the *MGMT* promoter was methylated. She went on to complete six weeks of concurrent TMZ with radiotherapy. Early on in her chemoradiotherapy course, the patient received one dose of bevacizumab. Unfortunately, her course was complicated by wound dehiscence soon after the completion of chemoradiotherapy. She underwent a repeat craniotomy with washout of the abscess, followed by 1 month of intravenous antibiotics. Subsequently, she started her first cycle of maintenance temozolomide. One month later, her infection recurred, and she restarted antibiotics. After another month of antibiotics, she started her second cycle of maintenance TMZ. She went on to complete six total cycles of maintenance TMZ without further infectious complications.

Soon after completing her sixth cycle, the patient started herself on an MSC blend at 40 mL twice daily. Approximately 2 months later, a new MRI was performed, which revealed significant involution of the contrast-enhancing portion of her tumor centered in the posterior corpus callosum, as well as new left hemispheric cerebral edema. Notably, records indicated that the patient had difficulty fully tapering off her antiepileptic medications between September 2019 and May 2020, which corresponds to the point at which her brain MRI initially demonstrated findings consistent with cerebral edema. However, 8 months later, a brain MRI revealed further regression of the tumor with resolution of the left hemispheric edema. MRI 4 months later demonstrated stability of the contrast-enhancing portion adjacent to the left ventricle [Figure 2]. As of the composition of this manuscript, the patient is doing well; 5 years and 3 months have elapsed since her diagnosis.

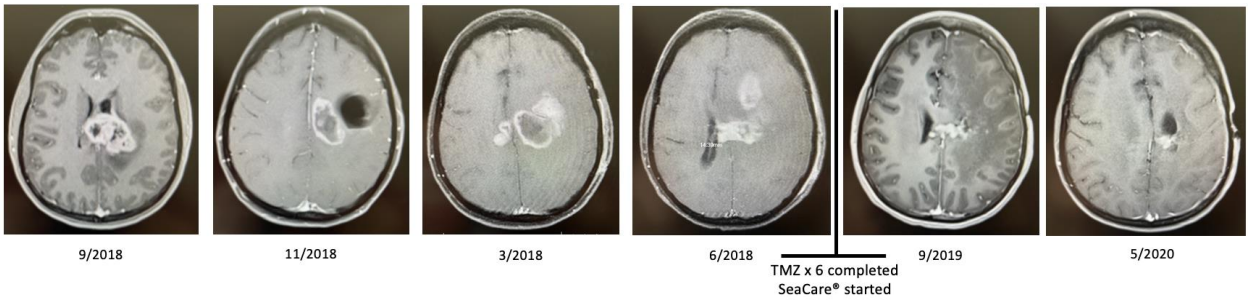

Figure 2. Serial radiographic response of Patient 2. Though the patient had a complicated clinical course, gadolinium-enhanced MRIs show a significant improvement in tumor size after completing 6 cycles of adjuvant TMZ and initiating marine nutraceutical products.

3. Discussion

3.1. Targeting the Tumor Immune Microenvironment in Glioblastoma and Immunomodulation of Tumor-Associated Macrophages

Glioblastoma remains the most common malignant primary brain neoplasm, with approximately 12,000 new cases diagnosed per year in the United States. It is considered largely incurable, with few therapeutic options. The median overall survival stands at 14.6 months, with a 5-year survival rate of 5.6% [3]. The current standard of care for newly diagnosed glioblastoma is maximal safe resection followed by concomitant radiation therapy with temozolomide (TMZ) and subsequent maintenance TMZ, with or without the addition of tumor-treating fields [4]. There remains a pressing need to improve outcomes in this patient population, and unique sources could yield critical breakthroughs.

The tumor immune microenvironment (TIME) has recently been the focus of extensive study. Characterizing the nuanced histologic architecture, diverse cellular composition, and complex metabolic processes of the TIME has offered significant insight into the molecular-level features that facilitate the growth and spread of neoplastic cells.

Immune cells have been identified as an important cell type in the TIME. The recruitment of immune cells into the TIME alerts the host to the presence of a tumor that it deems foreign. However, instead of interfering with the process of tumorigenesis as intended, host

immune cells in the TIME can be evaded, suppressed, or even exploited for carcinogenicity in response to local tumor influences [5,6].

Among the immune cell components of the TIME, tumor-associated macrophages (TAMs) represent a significant subset with key functions in the promotion of tumor growth, immunomodulation, and metastasis [7]. In the setting of glioblastoma, these macrophages comprise up to 50% of the total number of cells in glioblastoma [8]. The prominence of this population is important, as studies have shown that macrophages associated with glioblastoma may interact with glioblastoma stem cells (GSCs) and contribute to glioblastoma growth and migration [9].

Historically, two main macrophage phenotypic subclasses were identified and denoted 'M1-like' or 'M2-like', corresponding to pro-inflammatory or anti-inflammatory behavior, respectively. A variety of subclasses have since been identified and can more broadly be divided into pro-inflammatory (PI) or anti-inflammatory (AI) subtypes. The PI/AI phenotypes exhibit significant plasticity, and a switch from one phenotype to the other may occur in response to various stimuli. This process is called 'polarization', a term that reflects its transient and dynamic nature. The process of PI/AI polarization is complex and multifactorial. Infection or tissue damage, for example, may induce a shift to PI. PI cells then upregulate production of the enzyme inducible nitric oxide synthetase (iNOS) and its product, nitric oxide (NO), for their anti-microbial properties. A subsequent shift to the AI state can occur in response to temporal and environmental cues and serves to counteract persistence of the PI state and potentially excessive tissue damage. iNOS and NO may serve as biomarkers of pro-inflammatory PI activity, whereas arginase-1 (Arg-1) is a biomarker of anti-inflammatory AI activity [10].

Other components of various inflammatory pathways have also been identified in association with PI/AI polarization. Examples include cyclooxygenase-2 (COX-2) and nuclear factor kappa-light-chain-enhancer of activated B cells (NfkB). COX-2 inhibition prevents metastasis in certain tumors, and previous studies in murine models and in vitro have shown that downregulation of COX-2 inhibits AI macrophage differentiation and that the presence of COX-2 induces AI polarization [11,12]. NfkB has a variety of functions. It can induce PI differentiation and has been recognized as the major PI transcription factor, but it also plays a role in AI differentiation under the appropriate circumstances [13].

In general, TAMs have been shown to assume a largely AI phenotype and thus exhibit pro-neoplastic properties. In the context of gliomas, higher ratios of the subclasses M2/M1 were found in glioblastoma than in other gliomas and were found to correlate with glioma proliferation and mortality [14]. The concept of influencing the shift toward a PI phenotype therefore presents a potentially promising strategy for anticancer therapies [15], and several molecules with established immunomodulatory functions have demonstrated the ability to promote a shift toward an inflammatory phenotype [16–18].

Targeting macrophage phenotypic shifts is especially relevant when post-treatment effects on immunomodulation are considered. Given that radiation therapy for cancer is known to promote tissue damage, which can trigger macrophage phenotypic shifts, the effects of radiation on macrophage polarization have been investigated. Studies of macrophage populations in glioblastoma have shown that following ionizing radiotherapy, the total number of macrophages decreased, and in vivo studies have shown that the proportion of anti-inflammatory macrophages of the M2 subclass increased [19]. M1 subclass macrophages were also more sensitive to ionizing radiation when studied in vitro, potentially explaining the observed shift toward M2 [19]. Accordingly, while prior studies have shown differential stimulation of macrophage polarization depending on the dose of radiation, higher doses of radiation (>8 Gy) have been associated with a shift toward an anti-inflammatory macrophage phenotype [20]. Cumulatively, these data suggest that higher dosing of radiation, as used in the treatment of aggressive cancers like glioblastoma, may contribute to tumorigenic activity of the irradiated zone, in part through phenotypic modulation of the macrophage populations associated with these sites. This phenomenon

further demonstrates the potential for therapies that target phenotypic shifts toward PI/M1 macrophages to potentiate anti-tumor effects.

3.2. Tumor Immune Microenvironment Modulation and Other Anticancer Properties of Marine-Derived Therapeutics

Marine-derived products contain compounds that have shown activity against neoplastic processes at the cellular and molecular level and within the tumor microenvironment. Within this manuscript, we describe a series of patients that used a product called SeaCare®, which is known to contain an MSC blend and a smaller fraction of other marine-derived species. Specifically, it is composed of extracts derived from two separate species of sea cucumber, seagrass, sea squirt, and sea urchin [Table 2]. The majority of the product is made up of sea cucumber derivatives (85%). Various bioactive compounds that possess immunomodulatory capabilities and anticancer properties have been identified within each of the contained marine species [Table 1].

Table 1. FDA-approved marine-derived therapeutics. Important marine-derived compounds with clinical significance in cancer treatment are listed below alongside their marine source and the indication (cancer type) for which they were FDA-approved.

Drug	Marine Source	Indication (Year Approved)	Reference
Eribulin	Sea sponge (Halichondria)	Breast cancer (2010), liposarcoma (2016)	[21] [22]
Brentuxumab vedotin	Sea slug (Dolabella)	ALCL (2011) PTCL (2017)	[23] [24]
		cHL	[25]
Polatuzumab vedotin	Sea slug (Dolabella)	NHL (2019)	[26]
Enfortumab vedotin	Sea slug (Dolabella)	Urothelial carcinoma (2023)	[27]
Trabectedin	Sea squirt (Ecteinascidia)	Soft tissue sarcoma (2015)	[28]

ALCL, peripheral large cell lymphoma; PTCL: peripheral T-cell lymphoma; cHL, classic Hogkin's lymphoma, NHL, non-Hodgkin's lymphoma.

Table 2. Ingredient species list.

Name	Common Name	Phylum	Class	Order	Family	Genus	Species	Actual %
Sea Cucumber	Black Teatfish	Echinodermata	Holothuria	Holothuriida	Holothuriidae	*Holothuria*	*H. nobilis*	45
	Sandfish	Echinodermata	Holothuria	Holothuriida	Holothuriidae	*Holothuria*	*H. scabra*	40
Sargassum (whole plant)	Sea Weed	Heterokontophyta	Phaeophyceae	Fucales	Sagassaceae	*Sargassum*	*S. pallidum*	5
Sea Sponge	Sea Squirt	Chordata	Ascidiacea	Pleurogona	Styelidae	*Styela*	*S. clava*	5
Sea Urchin	Purple Sea Urchin	Echinodermata	Echinoidea	Camarodonta	Toxopneustidae	*Heliocidaris*	*H. erythro-gramma*	5

3.2.1. Sea Cucumber

Sea cucumbers are marine echinoderms, similar to starfish and sea urchins, with a wide geographic distribution. Their taxonomical classification is that of Holothuroidea, and there are over 1700 species. Holothuroidea can be found in shallow ocean waters off Southeast Asia and Oceania [29]. People of these regions have harvested sea cucumbers for both dietary and medicinal purposes for hundreds of years [30]. Anticancer properties of sea cucumber-derived triterpene glycosides have been recognized since the 1950s [31]. There are a number of bioactive compounds that can be found within sea cucumbers. Among them, the most well studied are triterpene glycosides. Triterpene glycosides belong

to a class of organic terpenes, which have a hydrocarbon backbone and typically contain multiple five-carbon ring structures. They contain both lipophilic and hydrophilic moieties, which influence their systemic bioavailability [32]. Those derived from sea cucumbers are known as holothurian triterpene glycosides [33].

A notable MSC-derived example is the compound TBL-12, which underwent preclinical testing in a prostate cancer cell model. In vivo, TBL-12 significantly inhibited tumor growth in a xenograft model of prostate cancer. In vitro, TBL-12 demonstrated activity in a range of cellular and molecular-level processes, including caspase activation to promote apoptosis and matrix metalloproteinase 2 and 9 (MMP2/MMP9) suppression to limit invasive potential, among others. Modulation of these pathways culminated in reduced proliferation, colony formation, and migration of prostate cancer cells [34].

With respect to glioblastoma, MMP9 has been shown to be an important regulator of treatment resistance and invasiveness. Studies have shown that tumor-associated macrophages (TAMs) express high levels of MMP9 [35]. Elevated levels of MMP9 expression in tumor specimens have been correlated with the biological aggressiveness of glioma cells [36]. Interestingly, irradiation of glioma cells both in vitro and in vivo increased the expression of MMP9 as well as the invasiveness of these cells. Studies using knockdown assays of MMP9 have demonstrated that the invasive potential of glioma cells can be significantly reduced while also decreasing radioresistance [37].

As stated above, sea cucumbers contain compounds that can block multiple tumorigenic pathways. Specific to the tumor immune microenvironment (TIME), a sea cucumber-derived triterpene glycoside isolate has demonstrated promising activity in inhibiting MMP9 as well as downregulating NfkB. The isolate, Ds-echinoside A, was shown to reduce the expression of MMP9 by almost 90% in a hepatocellular carcinoma cell line model. Additionally, NfkB levels were significantly reduced in the setting of Ds-echinoside A [38].

Another triterpene glycoside, known as holothurin A, which has been isolated from multiple species of sea cucumber, has also been shown to decrease the expression of MMP9 and vascular endothelial growth factor (VEGF), thereby inhibiting migration in hepatocellular carcinoma cell lines. Effects on NfkB have also been demonstrated [39]. Another example of triterpene glycoside biology and therapeutic potential is that of terminoside A, which has been demonstrated to inhibit the production of nitric oxide (NO) by downregulating the activity of inducible nitric oxide synthetase (iNOS). Terminoside A, which has been isolated from the bark of *Terminalia arjuna*, was shown to significantly reduce NO production by lipopolysaccharide-stimulated macrophages [40]. It is worth mentioning that the role of NO in cancer has been implicated in multiple tumorigenic pathways by mediating TAMs and local metabolic pathways (i.e., the Warburg effect) [10].

3.2.2. Seagrass

Seagrass-derived therapeutic compounds have also demonstrated the capacity to inhibit multiple pathways involving TAMs. A sulfated polysaccharide known as fucoidan isolated from brown seagrass, *Sargassum pallidum*, has been shown to promote apoptosis and inhibit epithelial-to-mesenchymal transition (EMT) by modulating a select subset of microRNAs, as well as upregulation of the E-cadherin pathway [41]. With respect to the tumor microenvironment, it is well established that EMT and the E-cadherin pathway are vital regulators of TAM macrophage biology. The upregulation of E-cadherin decreases the invasive potential of both neoplastic cells and TAMs, decreasing EMT in both entities [42,43].

Another important class of seagrass-derived therapeutic compounds are phlorotannins, which are a class of polyphenol molecules that are highly concentrated in the cell walls of many seagrass species, in particular, brown seaweeds such as the previously mentioned *S. pallidum* [44]. These unique compounds have been shown to have strong antioxidant properties [45]. phlorotannins have been shown to be scavengers of reactive oxygen species (ROS) and can inhibit other inflammatory pathways. A study evaluated the properties of phlorofucofuroeckol A, a phlorotannin derived from brown algae, and showed that

treatment with as little as 20 uM can strongly inhibit lipopolysaccharide (LPS)-induced production of inducible nitric oxide synthetase (iNOS) and cyclooxygenase-2 (COX-2). Additionally, the same study revealed that phlorofucofuroeckol A can inhibit the promoter activity of NfKB [46]. Furthermore, this class of polyphenol compounds has also been shown to modulate the immune system. Zhang et al. described that phlorotannins can recruit antigen presenting cells (i.e., dendritic cells) and promote cytotoxic T lymphocyte responses in animal models [47].

3.2.3. Sea Squirt

Sea squirts are part of a large group of ascidian marine invertebrate filter-feeders that are found in shallow portions of most of the world's oceans. Although there is a paucity of evidence suggesting direct immune modulatory capacity of the tumor microenvironment by sea squirt species, there is a very strong rationale for sea squirt-derived anticancer therapeutics.

Styela clava, a sea squirt native to the northwest Pacific Ocean, has been studied for its anticancer properties. the tunic (i.e., skin) of the *S. clava* has demonstrated potent anti-inflammatory properties through the modulation of the NfkB pathway. Chondroitin sulfate extracts from the tunic showed an ability to inhibit tumor necrosis factor (TNF)-alpha activation of NfkB. it was also shown to inhibit Akt signaling by suppressing the expression of iNOS [44]. As stated previously, both the NfkB pathway and overexpression of iNOS have been implicated in carcinogenesis.

In an in vitro model of human colon cancer, the sea squirt *Halocynthia roretzi* showed promising activity. Multiple mechanisms of apoptosis were activated via the caspase pathway, along with cell cycle arrest at the G2/M phase [48]. Another study from Zhu et al. revealed that the aqueous extract derived from *H. roretzi* significantly inhibited the Hep-G2 hepatocellular carcinoma cell line. Importantly, this study identified that a mixture of several different fatty amide groups may be most responsible for biologic activity. Furthermore, the combination of these extracts may be synergistic with doxorubicin, a commonly used chemotherapeutic. The combination was dose-dependent, with increasing concentrations of both *H. roretzi* extracts and doxorubicin yielding lower levels of cell viability [49].

Most notably, the sea squirt *Ecteinascidia turbinate* led to the discovery of trabectedin. The anticancer properties of *E. turbinate* had been known since the 1950s [50]. Eventually, the active ingredient was characterized and termed ET-743 [51]. Its structure was determined to be a tetrahydroisoquinoline alkaloid, and it demonstrated very potent anticancer activity in various preclinical models by modulating the DNA repair pathway [52,53]. Due to the overall low yield of ET-743 from marine-derived sea squirts, a semisynthetic method was used to produce what is now known as trabectedin [54]. In 2016, Demetri and colleagues published the results of a seminal randomized phase 3 trial, which assessed the safety and efficacy of trabectedin versus dacarbazine in patients with recurrent/refractory leiomyosarcoma or liposarcoma. The study found that trabectedin yielded better disease control compared to dacarbazine (4.2 months vs. 1.5 months); however, median overall survival between groups were not significantly different [28]. Subsequently, the Food and Drug Administration (FDA) approved trabectedin based on superior disease control in advanced refractory sarcoma, given limited standard options for this deadly malignancy [55].

3.2.4. Sea Urchin

There are over 900 species of sea urchin with a broad distribution across the world's oceans. Compounds derived from the sea urchin *Diadema savignyi* have shown promising activity against colorectal cell lines [56]. A study identified 19 compounds that had bioactive potential. Of those compounds, an organic compound belonging to the ergosterol family, known as brassicasterol, showed promising activity against a human colorectal cancer cell line (HCT116). Its biologic activity has been attributed to the downregulation of the Akt pathway, per Xu et al. [57].

Additionally, *D. savigny* has also shown potential neuroprotective properties in a rat model of cisplatin-induced neurotoxicity [58]. Cisplatin is a commonly used chemotherapeutic with an established risk of neurotoxicity especially to peripheral nerves.. In this in vivo study, extracts from the spines and shells of the urchin were prepared for testing. Animals were exposed to cisplatin over four weeks. Control animals exhibited clinical and biochemical signs of significant inflammation both in serum and in brain tissue samples. Those animals with exposure to sea urchin derivatives demonstrated normalization of multiple inflammatory markers, including nitric oxide.

Another sea urchin with potential therapeutic properties is *Stomopneustes variolaris*. A recent study demonstrated that the compound Stomopneulactone D from *S. variolaris* can significantly inhibit various inflammatory pathways, in particular COX-2 [59]. The study investigators isolated various macrocyclic lactones and tested these against LPS-stimulated macrophages. A subset of these compounds demonstrated very low micromolar inhibitory capacity of COX-2. Moreover, these compounds were highly selective and had strong inhibitory capacity when compared to ibuprofen. Inducible nitric oxide synthase was also strongly inhibited, further supporting the strong potential of sea urchin-derived compounds to inhibit multiple pathways of macrophage inflammatory response.

3.3. Clinical Experience with Majority Sea Cucumber Blend Therapeutics

Taking into account each individual marine-derived component found within SeaCare®, a multifactorial mechanism of action emerges that may explain a potential therapeutic benefit to this type of MSC blend. Given these data, it is reasonable to suspect that the majority of the therapeutic benefit may be derived from the sea cucumber ingredient since 85% of the product is composed of this; however, we cannot discount the potential for an additive effect from other ingredients found within the product.

The above supporting evidence brings to light both the in vivo and in vitro activity of triterpene glycosides that are found in the species of sea cucumber sourced specifically for SeaCare®. As discussed above, these glycosides have shown promising activity in modulating the TIME through various pathways that may strongly impact TAMs by inducing phenotypic shifts that promote tumor-hostile activity (i.e., pro-inflammatory macrophage differentiation or M1-subtype polarization). As described above, MMP9 plays an important role in TAM physiology as well as the overall invasiveness of glioma cells. The NfkB pathway is another target of triterpene glycosides. The importance of this pathway in TAM persistence cannot be understated, and given the ability of sea cucumber-derived triterpene glycosides to strongly inhibit this pathway, it may be an important contributor to its therapeutic effect. Additionally, by inhibiting inducible nitric oxide synthase, triterpene glycosides act on another vital pathway of M2-subtype (i.e., anti-inflammatory) pathogenesis within the TIME.

To a lesser extent, yet potentially as important, are the roles of fucoidan and phlorotanins derived from seagrass. These have been shown to inhibit similar pathways implicated in TAM biology, namely NfkB and iNOS. Additionally, phlorotanins can strongly inhibit COX-2, which has also been associated with TAM persistence within the TIME.

Modulation of the TIME using compounds derived from sea squirt and sea urchin have been less studied, comparatively. However, strong evidence exists that extracts from these marine invertebrates can have profound anticancer properties. sea squirts contain compounds that have been shown to directly inhibit cancer cells, with at least one derivative having gained FDA approval for the treatment of advanced refractory sarcoma. *S. clava* has also been demonstrated to modulate both NfkB and iNOS, which are important drivers of an immune-suppressed TIME.

Taken together, SeaCare® is a unique MSC blend with multiple active ingredients derived from sources that individually possess a biological basis for therapeutic benefit in cancer. To date, there has been at least one human clinical study that assessed the properties of an MSC blend therapeutic, known as TBL-12. This compound was manufactured by

the same company that manufactures and markets SeaCare® as a nutraceutical and food supplement.

In 2011, a phase 2 clinical trial of TBL-12 was initiated in subjects with untreated asymptomatic multiple myeloma (ASMM), known now as smoldering multiple myeloma (SMM) [60]. This condition is part of a spectrum of disorders known as plasma cell dyscrasias, which includes multiple myeloma. In 2011, the standard of care for most of these "asymptomatic" multiple myeloma patients was typically observation. Thus, TBL-12 was hypothesized to have a potential disease-modifying effect that could delay progression to multiple myeloma in this patient population.

The study enrolled a total of 20 subjects with ASMM that were diagnosed at a single institution. Subjects were provided TBL-12 as a liquid gel, which was kept frozen until consumption. Subjects were dosed with two units of 20 milliliters (mL) twice daily and continued on therapy until criteria were met for disease progression or intolerance. Compliance on the study was excellent, with minimal adverse events reported in a majority of subjects. A median of 15 cycles were administered (range 2–54). Interestingly, 18 out of 20 subjects remained alive since the publication of the study (2016), with a follow-up range of 16-72 months. The median progression-free survival for the 12 patients with active multiple myeloma was 11 months.

4. Conclusions

Glioblastoma is an aggressive and ultimately fatal neoplasm. Given its high rate of recurrence and mortality with current standard of care, the identification of novel therapeutic agents is critical. This case series illustrates the promising efficacy of marine-derived therapeutics in the treatment of glioblastoma, showcasing possible efficacy and an acceptable safety profile during concurrent chemoradiotherapy and as monotherapy. Herein, we hypothesized multiple mechanisms underlying these effects, with the common theme of modifying the tumor microenvironment at the cellular and molecular levels. These collective alterations appear to induce immunogenicity and mitigate tumor invasiveness, in turn possibly explaining the clinical benefit described in this case series. Taken together, this suggests a role for marine-derived products as potentially effective agents that warrant further study.

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