Bryostatin 1: Will the Oceans Provide a Cancer Cure?

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We are all aware that the rain forests have provided us with a large variety of natural products with wide-ranging medicinal powers. Although the oceans cover a large portion of the earth, it is not often that we think of them as a source of antineoplastic compounds. Bryostatin 1 is a compound derived from the marine bryozoan Bugula neritina of antineoplastic compounds. Bryostatin 1 is a compound that has a multiringed macrocyclic lactone structure derived from the sea that could inhibit tumor growth. The agent is derived from the marine bryozoan Bugula neritina by grinding and extensive purification. This bryozoan, a plate-like creature, forms multicellular aggregates that foul boats and docks (1,2). Bryostatin 1 is a family of more than 13 compounds that have a multiringed macrocyclic lactone structure with varying side chains. The sea bryozoan contains largely bryostatin 1, which has been the first member of this class of compounds to be tested in humans (3,4).

Like many compounds that appear promising but are found in animal studies to have a limited spectrum of antitumor activity, bryostatin 1 easily could have failed to be tested in humans had it not been for a serendipitous observation on cells in tissue culture. In the 1980s, the National Institutes of Health testing of bryostatin 1 in mice had shown excellent antitumor activity against murine P388 leukemia cells and the M5076 reticulum cell sarcoma but no effects on the treatment of mammary, colon, or lung cancer [results summarized in (5)]. However, in 1986, it was noted that incubation of bryostatin 1 with human leukemia cells stimulated the activity of protein kinase C (PKC) (6), an enzyme known to be involved in hormone-mediated signal transduction from the membrane to the nucleus and, thus, a regulator of cancer cell growth. Research (6,7) demonstrated that PKC activation mediated the activities of bryostatin 1 and that PKC was a bryostatin 1 cellular binding protein. Incubation of tumor cells with bryostatin 1 stimulated the activity of PKC (6), caused the association of PKC with both the cell membrane (6) and the nucleus (8), and eventually activated the degradation of PKC (9) through a still unknown mechanism.

PKC, an enzyme found in every human tissue and cell, is most highly expressed in the brain, spleen, and hematopoietic system (10). All forms of this enzyme are activated by changes in the cellular levels of specific phospholipids that are generated with the binding of hormones, while only specific isoforms are stimulated by changes in both phospholipids and intracellular calcium. Activated PKC, like other protein kinases, transfers the phosphate from adenosine triphosphate to acceptor proteins, thereby modulating their activity. PKC has been shown in the laboratory to be involved in such diverse processes as long-term memory, degranulation of neutrophils, muscle contraction, secretion of insulin, and, importantly, cell growth and differentiation (11,12). Overexpression of PKC alone is sufficient to transform certain specific types of tissue culture cells (13). The important role of PKC in mediating the effects of many different cellular processes suggests that bryostatin 1 might have wide-ranging biologic effects.

In culture, bryostatin 1 has been shown to induce the differentiation and halt the growth of human leukemia cells (7). This result has been demonstrated with fresh leukemia cells from the peripheral blood of patients with chronic myelogenous leukemia (14), chronic myelomonocytic leukemia (15), and acute myelogenous leukemia (16). B-lymphoma cells have been demonstrated to undergo differentiation after treatment with bryostatin 1 (17). Other elements of the hematopoietic system are also modulated by bryostatin 1. Bryostatin 1 induced platelet aggregation (18) and the oxidative burst of neutrophils (19). Moreover, when added to human bone marrow cultures, it stimulated the production of granulocyte—macrophage colonies (20). In culture, bryostatin 1 blocked cell—cell communication in epidermal cells (21) and the squamous differentiation of tracheobronchial epithelial cells (22) and inhibited the growth of human lung cells (23) and mammary carcinoma cells (24). In addition, studies have reported that bryostatin 1 enhanced the radioprotective effect of granulocyte—macrophage colony-stimulating factor on the bone marrow (25) and sensitized human cervical carcinoma cells to cisplatin (26). All of these laboratory studies predicted some important conclusions relevant to the first human trials:

1) The observation that short-term treatment with bryostatin 1 stimulated phosphorylation, but that long-term exposure markedly decreased PKC, suggested that the dose scheduling of this agent would be important.

2) Bryostatin 1 stimulated rapid degranulation of platelets and neutrophils, suggesting that bryostatin 1 infusion may have a potential deleterious side effect.

3) The ability of bryostatin 1 to modulate other chemotherapeutic and radioprotective agents suggests some unique properties separate from its direct antitumor activity.

Given the large number of bryostatin 1-induced biologic effects, the mechanism by which bryostatin 1 might kill human tumor cells in vivo could be quite complex. Bryostatin 1 has been shown to induce differentiation of leukemia cells (14-17), suggesting that tumors which have the potential to differentiate might respond to bryostatin 1 by cell differentiation. Bryostatin 1 could induce or inhibit the

*See "Notes" section following "References."
production of hormones by other tissues or organs that affect tumor growth. For example, in tissue culture, treatment of cultured cells with bryostatin 1 stimulated the release of tumor necrosis factor α (TNF-α), interferon γ, and interleukin 2 (27). These hormones might act in distant parts of the body to inhibit the growth of tumor cells. Also, bryostatin 1 might activate parts of the immune system to kill malignant cells. In the laboratory, bryostatin 1 has been shown to trigger the development of cytotoxic T lymphocytes (28,29). These expanded T lymphocytes have been used in a protocol of adoptive antitumor immunity (30). Further studies will be needed to define the mechanism of action of this agent in vivo and to determine whether the ability of bryostatin 1 to inhibit tumor growth either is a direct effect of this compound on tumor cells or is mediated by secreted hormones or whether the immune system plays a role.

In this issue of the Journal, Philip et al. (4) report on the first clinical trial of bryostatin 1. The major side effects of bryostatin 1 that these investigators demonstrated were myalgia and a transient and immediate fall in platelet counts, which returned to normal within 7 days. Other side effects included acute dyspnea and phlebitis; both of these side effects were most probably secondary to the vehicle in which bryostatin 1 was diluted. Unfortunately, because bryostatin 1 is insoluble in aqueous solutions (5), the vehicle necessary to deliver this compound will continue to be a problem. The fall in platelet counts reported by Philip et al. could be predicted from animal studies, but the myalgia that they observed was not previously reported. Since patients bothered by myalgia exhibited no obvious changes in electromyography or creatinine phosphokinase enzyme levels in the study by Philip et al., it might be instructive to know whether changes in PKC location, level, or activity induced by bryostatin 1 correlated with this muscle pain. At the highest level of bryostatin 1 given (50 μg/m2), Philip et al. observed statistically significant increases in both interleukin 6 and TNF-α levels, confirming data from cell culture experiments. The biologic importance of these transient increases remains unclear, since the two patients who showed a response to bryostatin 1 in the study by Philip et al. were given lower doses of bryostatin 1, thus stimulating low levels of hormone release. If low levels of hormone, either interleukin 6, TNF-α, or as yet unidentified factors, mediate tumor kill, then continuous infusion of bryostatin 1 may be the schedule to use. Further studies will need to be done in which patients are placed on more rigorously controlled escalating doses of this agent (something not done in this study) to determine whether release of these hormones does correlate with total dose of compound.

It is possible that bryostatin 1 may be active at low doses where it stimulates PKC but inactive at higher doses where it leads to the degradation of this signal transduction molecule. Because bryostatin 1 has many biologic effects, it will take some perseverance to determine the exact role that this compound will play in our chemotherapeutic armamentarium. This trial demonstrates that bryostatin 1 can be safely given with minimal side effects and can induce a tumor response.

References

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Notes

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