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Immune Modulators as Therapeutic Agents for Cutaneous T-Cell Lymphoma

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Abstract

Cutaneous T-cell lymphoma at all stages appears to be responsive to immune modulatory therapeutic approaches. We describe here the mechanistic rationale for the use of interferons, interleukin-12, retinoids, Toll-like receptor agonists, photopheresis and combinations of immune preserving, immune stimulatory therapies for CTCL.

Significant immune dysregulation characterizes the progression of cutaneous T-cell lymphoma (CTCL)(1). Substantial recent evidence indicates that soluble factors released by the malignant T-cell population may play an important role in the pathogenesis of the immune abnormalities. Increased production of Th2 cytokines, including IL-4, IL-5 and IL-10 has been observed and increased numbers of circulating regulatory T-cells (Tregs) producing transforming growth factor beta has been documented among some patients with Sezary syndrome(2). The end result of this is the depressed functions of multiple arms of the cellular immune response including decreased numbers and functions of circulating dendritic cells, and decreased numbers of cytotoxic T-cells and natural killer (NK) cells. All of these cell types are critical for the mounting of an adequate anti-tumor immune response.

Despite a declining cellular immune response in association with progressing CTCL, preservation of the host immune response along with the use of immune modulatory therapy remains an important treatment approach leading to significant clinical benefit, even for those with advanced CTCL. Moreover, those with early stage disease are particularly responsive to immune modulatory therapy.

In choosing the ideal immune modulator, a number of factors should be considered. Firstly, the agent should have the capacity to induce a robust anti-tumor immune response. The treatment should also directly produce high levels of apoptosis of the tumor cells. Finally, the ability to produce sustained immunologic memory against the tumor cells is of critical importance in an effort to produce prolonged clinical responses.

A number of cytokines that are products of cells of the innate immune system, including interferon (IFN) alpha, IFN gamma and IL-12 meet at least two of the above criteria with IFN alpha meeting all three. IFN alpha has been shown to produce high clinical response rates in some studies(3). It is clinically effective as a single agent for all stages of disease, with perhaps lower response rates among patients with large cell transformation or visceral disease. IFN alpha has multiple beneficial effects on the host immune response including activation of CD8+ T-cells and NK cells which are both putatively responsible for mediating direct anti-tumor cytotoxicity. IFN alpha also directly inhibits proliferation of the malignant T-cells in vitro as well as inducing apoptosis of the malignant cells. Because IFN alpha can activate CD8+ T-cells, it should be used with caution for patients with CD8+ CTCL.

Both recombinant IFN alpha as well as pegylated forms of IFN alpha, which has the advantage of a much longer half-life, have been successfully used for the treatment of CTCL(4). In low doses, adverse effects of therapy are generally well tolerated, although the elderly tolerate IFN alpha less well than younger individuals.

IFN gamma, a product largely of NK cells as well as CD8+ T-cells, is also a valuable therapeutic agent for CTCL(5,6). It too activates cytotoxic cells, but also has the added effect to enhance macrophage and dendritic cell activity. The ability to prime dendritic cells should be an important property for patients receiving photopheresis. IFN gamma can enhance the ability of antigen presenting cells to process the large numbers of apoptotic tumor cells that are generated as a result of the treatment. Moreover, IFN gamma can potentially prime antigen presenting cells to enhance IL-12 production which can further support a T-helper type 1 (Th1) response which is critical for optimal anti-tumor immunity(7).

IFN gamma also appears to be quite useful for patients with folliculotropic mycosis fungoides, particularly when it is combined with the topical Toll-like receptor (TLR) agonist imiquimod(AH Rook, unpublished observations). IFN gamma appears to synergize with multiple different TLR agonists in its ability to stimulate IL-12 production(8). This has been shown to be the case in vitro using peripheral blood cells of patients with Sezary syndrome(7).

A distinct advantage that IFN gamma possesses over IFN alpha is a lower frequency of adverse effects on the cognitive abilities of the elderly. IFN gamma may also less frequently cause or aggravate depression in comparison to IFN alpha.

IL-12, a product of myeloid dendritic cells and monocytes, is another cytokine that has been demonstrated in phase I and phase II clinical trials to provide clinical benefit for patients with CTCL(9,10). As IL-12 does not directly inhibit the growth of malignant CD4+ T-cells of Sezary syndrome patients, it presumably mediates its beneficial effect through the enhancement of cytotoxic T-cell and NK cell activities and through the induction of IFN gamma by NK cells. Direct infiltration of regressing CTCL lesions with cytotoxic T-cells with concomitant tumor cell apoptosis has been observed during IL-12 therapy(9). The phenomenon of cytotoxic T-cell infiltration within CTCL skin lesions has also been observed in a recent clinical trial using IFN gamma(AH Rook, unpublished observations). This likely is also an effect of IFN alpha. Thus, the ability of each of these cytokines to activate and to mediate cytotoxic T-cell responses is of critical importance. As our advanced stage patients who appear to have the most sustained clinical responses to therapy have typically received an immune potentiating cytokine in the interferon family, this should be advocated for such patients as frontline therapy.

Interleukin 21 is another immune potentiating cytokine that is currently in clinical development for the treatment of a number of malignancies including metastatic melanoma

for which clinical activity has been observed. It has the ability to potentially activate NK cells and CD8+ T-cells. Recent studies have demonstrated that IL-21 can enhance the immunological functions of both NK cells and CD8+ T-cells derived from the peripheral blood of patients with Sezary syndrome(11). Moreover, IL-21 can augment the ability of immune cells from these patients to directly kill malignant T-cells in vitro(11). These in vitro observations, along with the clinical trial results for metastatic melanoma, suggest that IL-21 would likely be an active therapeutic for CTCL.

Systemic retinoids also represent a desirable first-line therapeutic choice for CTCL as they are therapeutically active and do not blunt the immune response. Bexarotene, which produces response rates approaching 50% for both early and late stage CTCL, has the ability to induce tumor cell apoptosis and to inhibit IL-4 secretion from the patients' T-lymphocytes(12). Bexarotene also appears to inhibit expression on the malignant T-cells of certain chemokine receptors, particularly CCR4, that are critical for permitting the cells to gain access to the skin(13). In concert with the inhibition of expression of CCR4, is the blunting of chemotaxis of the bexarotene treated malignant T-cells in response to the chemokine TARC (CCL17) which is the epidermal derived ligand for CCR4(13). Thus, bexarotene appears to exert multiple beneficial effects in the therapy of CTCL.

It is noteworthy, however, that some patients can become resistant to bexarotene therapy. We have identified among some bexarotene treated patients the subsequent outgrowth of circulating malignant T-cell clones that lack RXR receptors which may preclude the binding and pro-apoptotic effects of bexarotene(14). Although these patients were clearly sensitive to therapy at the outset, with bexarotene manifesting pro-apoptotic effects on their malignant T-cells, they ultimately manifested disease progression in association with in vitro resistance of the their malignant T-cells to bexarotene induced apoptosis(14; and AH Rook, unpublished observations).

The findings of bexarotene resistance represents an important basis for employing multimodality immune based regimens in an effort to target the malignant T-cells with agents that exert different mechanisms of action of tumor cell killing. Thus, we frequently combine bexarotene with an interferon, or with photopheresis or both, particularly for patients with leukemic variants of CTCL. Bexarotene can also be a useful therapeutic adjunct for patients receiving phototherapy. Combining interferons with phototherapy can also represent a useful approach with an increased rate of therapeutic efficacy.

There is also emerging evidence that Toll-like receptor (TLR) agonists represent a class of therapeutic agents that may prove to be highly effective for CTCL, even among those with advanced stage disease(15). It has long been known that topical imiquimod, a TLR 7 agonist, has the ability to activate the local cutaneous immune response in and around malignant lesions resulting in the regression of CTCL patches and plaques(16). Responses may be quite variable based upon the low bioavailability of imiquimod. Some patients may have quite low numbers of TLR 7 expressing cutaneous plasmacytoid dendritic cells, particularly if they have recently used skin directed therapies that may diminish numbers of these cells, including topical steroids, PUVA or radiation therapy. Resiquimod, which is under clinical development, has a much higher level of bioavailability, and, thus, may produce substantially higher response rates than imiquimod. Furthermore, resiquimod triggers TLR 8 in addition to TLR 7. The ability to trigger TLR 8 carries the advantage of the potential to activate myeloid dendritic cells which are potent producers of IL-12.

Clinical trials have begun with parenterally administered TLR agonists. Recently, a phase I trial using a type B CpG, which triggers plasmacytoid dendritic cells which bear TLR 9, demonstrated efficacy among patients who were highly pretreated and refractory to multiple

therapies(15). Several patients in the trial with advanced stage CTCL refractory to multiple systemic therapies experienced complete clinical responses. Moreover, we have demonstrated that CpGs in vitro can potently activate NK cells and cytotoxic T-cells of patients with Sezary syndrome(17). Thus, since CpGs can activate cytotoxic T-cells leading to an enhanced antigen specific cytotoxic T-cell response, this family of compounds is likely to represent an active additional component of a multimodality immune modulatory approach.

In this regard, CpGs and other TLR agonists are likely to augment the response rates achieved with extracorporeal photopheresis. Our center has found photopheresis to be particularly useful for patients with leukemic involvement. Although photopheresis may be used as monotherapy, it is important to stress that multiple groups have observed higher response rates when photopheresis was combined with immune adjuvants such as interferons, retinoids or granulocyte-macrophage colony stimulating factor(18). TLR agonists have not yet been tested with photopheresis. Nevertheless, activation of antigen presenting cells (APCs) by TLR agonists would likely represent a beneficial effect as APC processing of the photopheresis treated T-cells is a critical part of the efferent response to photopheresis. Moreover, as described above, TLR agonists are powerful activators of what would be considered the efferent response to photopheresis, specifically the activation of NK cells and cytotoxic T-cells, both of which can lyse malignant T-cells. Thus, clinical trials of TLR agonists with photopheresis for leukemic variants of CTCL should be considered highly desirable.

Photopheresis used in combination with other immune augmenting agents has resulted in clinical remission in nearly 30% of our patients with Sezary syndrome along with partial responses among another 50%. These high response rates should suggest a bright future for the continued development of new immune modulatory agents. Our therapeutic “wish list” presently includes IL-12, IL-21 and TLR agonists. Other novel approaches which harness the immune response should include anti-T-cell vaccination and efforts to develop targeted therapeutics which preserve the host immune response. Much work remains to be accomplished.

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Table I**Immune Modulatory and Biologic Therapies for Cutaneous T-Cell Lymphoma**

Agents in the clinic	Interferon alpha Interferon gamma Retinoids Photopheresis GM-CSF Imiquimod
Agents in development	IL-12 IL-21 TLR agonists (Resiquimod, CpGs) Dendritic cell vaccines