Interferons in cutaneous T-cell lymphomas

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A B S T R A C T

Cutaneous lymphomas are a heterogeneous group of rare lymphoproliferative disorders. In most cases, they are characterized by the accumulation of clonal lymphocytes in the skin. Extracutaneous involvement is present in late stages only. Unfortunately, only few drugs are registered for these disfiguring diseases. Skin directed therapies using topical formulations are the preferred first line modalities. Interferon alpha and Interferon gamma are successfully used as monotherapy or as important substances in combination therapies for cutaneous t-cell lymphomas. An intralesional therapy with Interferon alpha is very successful in primary cutaneous B-cell lymphomas, especially marginal zone lymphomas. Recent approaches using gene therapy resulting in local expression of Interferon gamma have resulted in the regression of injected and non-injected lymphoma manifestations in cutaneous lymphoma patients.

Both, T and B-cell lymphomas can involve the skin, either primarily or secondarily. Primary cutaneous lymphomas refer to neoplasms that are present in the skin with no evidence of extracutaneous disease at the time of diagnosis. The skin is the second most common site of extranodal Non-Hodgkin lymphomas after the gastrointestinal tract with an estimated annual incidence of 1/100,000.

Primary cutaneous lymphomas typically demonstrate a clinical behaviour differing from that of the histologically similar nodal lymphomas, which may involve the skin secondarily. Therefore, it makes sense to classify cutaneous Non-Hodgkin lymphomas separately from other Non-Hodgkin lymphomas. This has been achieved with the EORTC-WHO classification for tumors of hematopoietic and lymphoid origin.[1] Most CTCL are indolent neoplasms with a very wide variation in clinical presentations. In early stages, they affect the quality of life due to their impact on skin appearance and annoying symptoms such as pruritus. In some cases, depending on the quality of skin involvement and the areas involved, they can already be disfiguring in early disease stages. In advanced stages, local skin problems are accompanied by systemic deviations of the immune reaction pattern which result in an increased risk of infections and secondary malignancies. It is important to note that some of the late stage problems in CTCL patients might have been aggravated by earlier therapeutic interventions. For example radiotherapy or phototherapy may contribute to mutations that increase the proliferative and invasive capacity of the tumor cell populations. Most patients with advanced disease do not die due to lymphoma manifestations but due to secondary problems such as infections.

The patient population suffering from CTCL is of advanced age. These patients have many concomitant medical problems such as hypertension, heart failure, diabetes and other diseases. Since current literature does not demonstrate any curative treatment options, a realistic goal for CL treatment is to achieve long lasting remissions in a significant percentage of patients with drugs that can be safely used over a certain period of time without long-term toxicity.

Despite intensive research including modern molecular biology techniques such as gene expression arrays, the molecular differences between tumor cell populations and benign CD4 lymphocytes remain obscure. As there are many small molecules that interfere with signal transduction cascades, it is important to define the molecular events that are crucial to the survival and growth of neoplastic populations. Hopefully, precise information on the defects in individual patients will even-

tually allow specifically tailored molecular interventions. One possible approach is the application of replicating viruses in patients with tumor cell clones deficient in interferon signalling. Replicating viruses can be safely used in vitro to target tumor cell populations.[2]

CTCL are characterized by an accumulation of clonal T-lymphocytes in the cutaneous microenvironment. It is assumed that the epidermal and dermal compartments provide essential signals for the survival and proliferation of the T-cell clones. The malignant T-cell populations are well differentiated mature cells that still have the capacity to regulate immune functions. Based on our information of the cytokine profile and phenotype, they are T-helper memory cells predominantly displaying T-helper-2 cytokines such as interleukin (IL)-10, resulting in local and systemic dysbalance of the T-helper-1/T-helper-2 system. Based on this concept therapeutic approaches try to target the tumor cells in the dermal compartment or to correct immune deviations.

Re-storing depressed T-helper-1 effector functions locally and systemically

The clinical course of CTCL is accompanied by a dysregulated synthesis of cytokines. As was recently reviewed,[3] cytokines can influence tumor cells in an autocrine, paracrine and endocrine fashion.

Antibodies against Vα/β of the TCR malignant T-cell clones from SS patients were purified. Their phenotypes were $CD3^+$, $CD4^+$, $CD5^+$, $CD45RO^+$,[4,5] comparable with peripheral T memory cells. In situ, IL-10 protein co-localizes with expression of the non-classical HLA molecule HLA-G.[6] HLA-G is able to inhibit cytotoxic cells such as cytotoxic CD8+ cells or NK-cells.

IL-10 indirectly prevents antigen-specific T cell activation, which is in turn associated with the down-regulation of antigen presentation and accessory cell functions in monocytes, macrophages, Langerhans and dendritic cells. In addition, IL-10 limits T cell expansion by directly inhibiting IL-2 production by these cells.[7,8]

Since TH1 cells are the principle effectors of cell-mediated immunity against tumor cells and delayed-type hypersensitivity reactions, it seems to be an advantage for malignant cells to switch the immune response of the host to a TH2 type.[9] This switch is suspected because of the IL-10 transcription, secretion of reactive non-clonal T cells and the lack of IL-2 and IFN-γ transcription in non-sorted PBMC of SS patients.[10] The dominance of the TH2 cells probably explains the well-known clinical phenomena seen in SS patients and other CTCL patients, such as reduced cutaneous delayed-type hypersensitivity reactions, hypereosinophilia, alterations in serum immunoglobulin levels (IgE, IgA) and an increased risk of second malignancies and immunological abnormalities of PBMC such as reduced natural killer cell activity and decreased mitogen-induced proliferation.[11]

Based on these findings, approaches that increase the activity of T-helper-1 responses are promising for the therapy of CTCL. Interferons can help to reach this aim.

Local IFN induction by the toll-like receptor agonist: imiqimod

Imiquimod (1 (2 methylpropyl)-1*H*-imidazo [4,5-*c*]quinolin-4-amine) belongs to the group of imidazoquinolones, synthetic local immune response modifiers that have demonstrated potent antiviral and antitumor activity. Imiquimod activates macrophages and other monocyte-derived immune cells via interaction with toll-like receptor (TLR)-7, inducing the local production of cytokines such as interferon (IFN) α, tumor necrosis factor (TNF) α, and IL-12 and resulting in an enhanced innate immune response. In addition, imiquimod induces migration and activation of skin Langerhans' cells ,[12]all of which promotes the biasing of naïve T cells to Th1 cells, which are potent producers of IFN-γ, thus leading to the enhancement of adaptive immunity. The stimulation of innate and adaptive immunity may finally lead to the regression of viral-induced lesions and neoplasms. Imiquimod has been tested and found to be effective in clearing superficial epithelial cancers such as basal carcinomas and actinic keratoses.

There are few case reports that suggest an antitumor effect of imiquimod in CTCL. Imiquimod was mainly used in patch stage Mycosis fungoides. There are some smaller phase II trials underway to investigate the role of imiquimod in the treatment of early stage CTCL.[13,14,15]

Adeno-IFN-gamma (TG1042)

TG1042 was investigated in a phase I, open-labelled, dose-escalating trial of repeated, intratumoral administration of TG1042 in patients with advanced primary CTCL and multilesional cutaneous B cell lymphomas (CBCL). TG1042 is a third generation, non-replicating (E1 and E3 regions deleted) human adenovirus vector con-

taining human IFN-γ cDNA insert. Nine patients (7 CTCL, 2 CBCL) were enrolled in 3 successive cohorts at the following TG1042 doses: $3{\cdot}10^9$, $3{\cdot}10^{10}$, and $3{\cdot}10^{11}$ total particles. Local clinical response was observed in 5/9 patients that received intratumoral TG1042 injections [3 patients with complete (CR) and 2 patients with partial response (PR)]. Out of these, 3 patients showed systemic CR, with the clearance of other non-injected skin lesions. Clinical response lasted for a median of 3 months (range 1-6 mo). Adverse events were mostly of grade 1 and 2. 7/9 treated patients had detectable TG1042-derived IFN-γ message in injected lesions after the first treatment cycle. TG1042-IFN-γ message was also detectable after several treatment cycles. In addition to local immune activation, the induction of humoral immune responses to lymphoma tumor-antigen se70-2 suggests a systemic effect.[16]

Based on the promising phase I clinical data, TG1042 is now being tested in international phase II clinical trials in CTCL and CBCL.

IFN- alpha and PEG-IFN-alpha

Alpha-interferon is known to activate immune responses including natural killer cell and macrophage activity and has been successfully used in CTCL for more than a decade.

However, interferon therapy is associated with a dose-dependent toxicity and its administration is further complicated by its short half-life, requiring at least three weekly subcutaneous administrations. Each post-injection peak in serum concentrations causes acute influenza-like symptoms (including fever, chills, myalgia, headache and arthralgia). Repeated injections may induce liver abnormalities, hematological toxicities and, most commonly, fatigue, which can hamper long-term treatment. These side effects are often severe enough to prompt dose reductions resulting in patients receiving less than the target dose.

PEG-IFNα-2a is a form of recombinant human IFNα-2, modified by the covalent attachment of a branched 40KD methoxypolyethylene glycol moiety. Already licensed for use in chronic hepatitis C, studies in this population found that PEG-IFNα-2a has superior efficacy to non-pegylated IFNα, with its long half-life allowing a more convenient, once weekly dosing regimen. Phase I and II clinical studies have been conducted with PEG-IFNα in renal cell carcinoma and chronic myelogenous leukemia.[17] Since it is not exactly known how PEG-IFNα-2a is tolerated in CTCL patients, a phase I dose escalation trial was recently begun.

IFN-gamma

IFN-gamma is a homodimeric cytokine which is produced mainly by T-helper-1 lymphocytes and natural killer cells. It is available for clinical use as a recombinant protein and as a natural human molecule. It was launched for the treatment of Mycosis fungoides in Japan in 1997 and is approved for adult T-cell leukemia (ATL). There are several case reports that claim that intralesional injections of gamma-IFN can induce lasting remissions.

Conclusion

Interferon alpha and interferon gamma have proven their efficacy in primary cutaneous lymphomas. They are important treatment options since they do not result in immunosuppression in cutaneous lymphoma patients. New developments such as pegylated Interferons and gene therapy mediated approaches now offer a new perspective for immunotherapy using this pleiotropic cytocine.

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