Topical Treatment of Cutaneous T-cell Lymphoma Skin Lesions with the Mouse Anti-CD6 Monoclonal Antibody IOR-T1

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ABSTRACT

Cutaneous T-cell lymphoma (CTCL) is a group of neoplastic diseases characterized by malignant T-lymphocyte skin infiltrates, with a poor response to conventional therapy. Monoclonal antibodies (MAbs) against T-cell differentiation antigens have been used as experimental modalities of treatment in these diseases, with brief antitumor responses.

IOR-T1 is an IgG2a mouse anti-CD6 MAb that identifies a majority of CTCL malignant T-lymphocytes, and does not induce the modulation of the antigen. In the present study we report the regression of skin limited plaques in three CTCL patients that were treated topically with a neutral hydrophilic cream containing 3 mg/g of IOR-T1, three times/day, for a month. No effect was seen in similar lesions when either an anti-carcinoembryonic antigen MAb, or placebo (cream alone) were used.

The design of this study and its results indicate that IOR-T1 is absorbed through the skin, and produces important clinical changes in CTCL lesions, compatible with an objective antitumoral effect. Overall, our results suggest that topical application of MAbs in malignant skin lesions could provide a new adjuvant therapeutic modality in CTCL.

RESUMEN

Los linfomas cutáneos a células T (CTCL) constituyen un grupo de enfermedades neoplásicas caracterizadas por infiltrados de células T malignas en piel, con una pobre respuesta a la terapia convencional. La aplicación intravenosa de anticuerpos monoclonales (AcM) contra antígenos de diferenciación de células T ha sido experimentalmente evaluada como modalidad terapéutica en estas enfermedades, con respuestas antitumorales limitadas.

El IOR-T1 es un AcM de ratón del isotipo IgG2a dirigido contra el antígeno CD6. Este AcM identifica una alta proporción de células T malignas en pacientes con CTCL y no induce la modulación del antígeno. En el presente artículo reportamos la regresión de placas cutáneas limitadas en tres pacientes de CTCL que fueron tratados con una crema neutra hidrofílica que contenía 3 mg/g de IOR-T1. La crema fue aplicada tres veces al día durante un mes. En lesiones similares de estos pacientes, tratadas con un AcM anti antígeno carcinoembrionario, o placebo (sólo crema), no se observó efecto alguno sobre las características de las lesiones.

El diseño de este estudio y sus resultados indican que el IOR-T1 es absorbido a través de la piel y produce importantes cambios en las lesiones, compatibles con una respuesta antitumoral objetiva. Nuestros resultados sugieren la posibilidad de que la aplicación tópica de AcM pueda convertirse en una nueva modalidad terapéutica adyuvante en CTCL.

INTRODUCTION

Sézary Syndrome and Mycosis Fungoides are malignant states classified as cutaneous T-cell lymphomas (CTCL), a group of diseases characterized by a monoclonal...
Treatment of CTCL with the IOR-T1 MAb

The expansion of T lymphocytes, with a marked skin tropism. Sézary Syndrome shows a preferential peripheral blood presentation, while Mycosis Fungoides is characterized by a scaly eruption that progresses through a plaque stage leading to skin tumors (Broder and Bunn 1980; Haynes et al., 1981; Kung et al., 1981; Miedena et al., 1984). CTCL tumor cells are negative for thymus antigen and identical in phenotype to the subset of normal helper T cells, a fact that suggests that in this disease the malignant cells are derived from mature, well differentiated T lymphocytes (Haynes et al., 1981; Kung et al., 1981).

As conventional therapeutic modalities produce very limited remissions in CTCL patients (Knobler and Edelson 1986), efforts have been conducted for the establishment of new experimental treatment variants. Among these, serotherapy with specific monoclonal antibodies (MAbs) represents a theoretically attractive therapeutic approach, due to its specificity and low probability of colateral toxicity (Ritz and Schlossman 1982; Oldham 1983; Dillman 1984; Press et al., 1987). In fact, it has been shown that the infusion of MAbs against lymphoid cell differentiation antigens is well tolerated (Miller et al., 1983; Meeker et al., 1985). Moreover, the T-cell differentiation antigens phenotype of malignant peripheral blood cells from CTCL patients is remarkably homogeneous.

Miller and Levy (1981) described a striking antitumoral response following the intravenous administration of MAb Leu.1 (anti-CD5) in a patient with CTCL, and tumor regressions lasting from 1.5 to 4 months in five additional patients treated with the same MAb (Miller et al., 1983). On the other hand, Dillman et al. (1985, 1986) have reported that the intravenous infusion of MAb T101 in 10 CTCL patients only resulted in brief antitumoral responses, lasting from days to weeks in 4 of the cases. Finally, Bertrand et al. (1986) used this same MAb in 8 patients, with a partial response in the cutaneous lesions of one case, which persisted for 3 months.

The mouse IgG2a MAb IOR-T1 was obtained after the immunization of BALB/c mice with peripheral blood lymphocytes of a patient with Sézary Syndrome (Garcia et al., 1984). This MAb recognizes the CD6 antigen, present in the surface of CTCL malignant lymphocytes (Rodriguez et al., 1985). In this paper we show that the topical treatment of skin lesions in CTCL patients with a cream containing IOR-T1 leads to objective tumor regressions.

MATERIAL AND METHODS

Patients

Three adult patients with clinically- and histologically-confirmed CTCL were included in the study. All patients were staged as III B, according to the TNM classification (Bunn and Lambert, 1979), and had not received specific oncological treatment for at least one month before the application of MAbs. The trial was performed under the rules and protocols approved by the Scientific Committee of the National Institute of Oncology and Radiobiology of Havana, with written consent from all patients.

Monoclonal Antibodies

IOR-T1 is an IgG2a mouse MAb that reacts with a 120 kDa human lymphocyte differentiation antigen (CD6), expressed in T lymphocytes and B-CLL malignant cells (Garcia et al., 1984, 1989; Rodriguez et al., 1985).

| IOR-CEA.4 is an IgG1 mouse MAb that recognizes the carcinoembryonic antigen (Gavilondo et al., 1987). |
| MAbs were produced at high specific concentration in the ascites of Pristane-primed BALB/c mice, after the intraperitoneal inoculation of hybridoma cells. |
| For therapeutic use, clarified ascites was precipitated with ammonium sulphate, dialyzed extensively against phosphate buffered saline, and sterilized by sequential 0.2 and 0.1 μm filtrations. After determination of protein and mouse IgG concentrations, the samples were stored at -70°C until use. |
| Fresh weekly batches of therapeutic cream were prepared by adding 3 mg of MAb per gram of neutral hydrophilic base cream. |
Treatment Schedule

In each patient, three limited plaques with complete skin integrity, and of similar and well defined extension, were selected and treated either with the IOR-T1, IOR-CEA.4, or placebo (no MAb) creams, three times per day, during one month.

Criteria of Response

Changes in the following clinical parameters were evaluated in the lesions: erythema, flattening, diameter, roughness, desquamation, and pruritus. Other visible alterations were also recorded for analysis. On such basis, the outcome of the study was classified as: (a) complete response (CR), when all measurable disease disappeared, (b) partial response (PR), when a decrease of at least 50% of the clinical characteristics of the lesion was noted, and (c) stabilization (S), when no detectable changes were recorded, or a 25% increment was seen in the clinical characteristics of the lesion. Response was evaluated within a period of four weeks after finishing the treatment.

RESULTS AND DISCUSSION

The IOR-T1 MAb was selected for this study due to several favorable characteristics. First, it recognizes an antigen present in a high proportion of peripheral malignant lymphoid cells from Sézary Syndrome patients, as well as in cutaneous malignant infiltrates from Mycosis Fungoides (García et al., 1984; Rodríguez et al., 1985). Second, the 120 kDa surface differentiation antigen (CD6) identified by IOR-T1 does not modulate its expression after antibody binding (results not shown). Finally, this MAb has a IgG2a isotype, a characteristic that has been claimed as adequate for MAb serotherapy in other studies (Herlyn et al., 1985).

This paper is the first of a series of reports of current therapeutic evaluations and trials of IOR-T1 in CTCL, using both topical and intravenous administration. The singular skin tropism of CTCL provided us with the particular possibility of first evaluating the effects of IOR-T1 without the need of parenteral infusions. Alternative to intralesional injection, we chose topical application. To our knowledge, no previous published study had employed such route, and the penetration of antibody through the skin surrounding tumors had not been documented. A neutral hydrophilic cream was chosen as vehicle, and the amount of antibody was first selected empirically, on the basis of the largest quantity that could be mixed properly.

The Table summarizes the response of the skin lesions to the topical treatment with IOR-T1, IOR-CEA.4 or placebo. As shown, only the lesions treated with IOR-T1 experienced an objective response in all patients; two of the three patients had a complete response, and the third a partial response. The fast disappearance of pruritus was followed by a progressive decrease in roughness, and elimination of desquamation. Regression within the lesions started from the periphery towards the center, until all signs of tumor burden disappeared (Figure 1).

Table

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>MAb IOR-T1</th>
<th>MAb IOR-CEA.4</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/M</td>
<td>CR</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>76/F</td>
<td>CR</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>69/M</td>
<td>PR</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>

Response 3/3 0/3 0/3

Note: MAb = monoclonal antibody (in neutral hydrophilic cream); Placebo = cream alone; CR = complete response; PR = partial response; S = stabilization. See text for details on response criteria.
FIG. 1. Effect of topical treatment with MAb IOR-T1 in skin lesions of a CTCL patient: (a) malignant lesion with moderate infiltrated plaques of irregular and well delimited shape, before treatment; (b) the same area after 1 month of application of IOR-T1. All signs of malignant activity have disappeared.
The design of this study and its results suggest that IOR-T1 is absorbed through the skin, and produces important clinical changes in CTCL lesions, compatible with an objective antitumoral effect. Subsequent histological studies in a new series of patients have shown that, after IOR-T1 topical treatment, CD6+ cells within the skin tumors disappear simultaneously with the clinical manifestations of the lesion (manuscript in preparation).

Mechanisms by which unmodified MAbS can induce the removal of tumor cells in vivo remain controversial. Most authors currently propose antibody-dependent cellular cytotoxicity, and phagocytosis by the reticuloendothelial system of MAb-coated cells as the main mechanisms involved (Dillman, 1984; Adams et al., 1984). Overall, our results with IOR-T1 suggest that topical application of MAbS in malignant skin lesions could provide a new adjuvant therapeutic modality.

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REFERENCES


