Biological Treatment of NSCLC*

The Need for Conclusive Studies

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Despite extensive investigation, biological treatments for non-small cell lung cancer (NSCLC) remain largely undeveloped. The lack of satisfactory models has frequently led to inadequate phase II studies and to small and inconclusive phase III trials. Nonuniformity of trials has prevented clearer conclusions from being reached by meta-analysis. In general, immunotherapy has failed to fulfill expectations for clinical usefulness. The benefit with this approach, if any, seems to be marginal, but it is not clear whether this is a result of lack of activity or faulty clinical testing. The future of biological agents in cancer treatment lies in ongoing advances in molecular biology, for example in making tumors more immunogenic. Another avenue of further clinical research includes novel forms of therapy with monoclonal antibodies. Adequate models for testing and appropriate clinical trial settings could clarify the role of biological agents in NSCLC.

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Several therapies aimed at restoring or enhancing immune functions have been explored in patients with non-small cell lung cancer (NSCLC). These approaches have included active nonspecific, active specific, adoptive, and passive immunotherapy. In some studies, modest beneficial effects have been observed, though the results have generally been conflicting. Small patient samples as well as great differences between studies, in the type of agent used, dose, and the route of delivery, have made interpretation of the results difficult. This article reviews the trials that are most often cited and will mention possible avenues for future studies.

Active Nonspecific Immunotherapy

Most active nonspecific approaches to immunotherapy have included the use of bacillus Calmette-Guérin (BCG) or other bacterial vaccines, levamisole, interferons (IFNs), and interleukins (ILs). Of the trials using BCG as an adjuvant to surgery (Table 1),1,3 most,4,6,9 including all with an adequate number of patients,3,4,6,8 showed no improvement with BCG vaccination as compared with nonimmunized control subjects. In most of the trials,1-5,7 BCG was given intrapleurally after surgery. In one study,5 it was combined with intradermal application; other studies involved subdermal,6 oral,8 or preoperative intratumoral9 BCG application. No conclusion on the optimal route of administration could be established. Negative outcome with BCG vaccination has resulted in decreased interest in further testing of this agent in NSCLC.

Table 1—Results of Adjuvant BCG Trials in the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Source</th>
<th>Mode of Administration</th>
<th>No. of Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>McKneally et al1</td>
<td>Intrapleural</td>
<td>169</td>
<td>Lower incidence of recurrence in stage I; no benefit for stage II and III</td>
</tr>
<tr>
<td>Lowe et al2</td>
<td>Intrapleural</td>
<td>92</td>
<td>No benefit</td>
</tr>
<tr>
<td>Mountain and Gail3</td>
<td>Intrapleural</td>
<td>425</td>
<td>No benefit</td>
</tr>
<tr>
<td>Ludwig group4</td>
<td>Intrapleural</td>
<td>441</td>
<td>No benefit</td>
</tr>
<tr>
<td>Jansen et al5</td>
<td>Intrapleural ± intrapleural</td>
<td>54</td>
<td>Improved recurrence-free survival</td>
</tr>
<tr>
<td>Edwards5</td>
<td>Subdermal</td>
<td>500</td>
<td>No benefit</td>
</tr>
<tr>
<td>Millar et al7</td>
<td>Intrapleural</td>
<td>97</td>
<td>No benefit</td>
</tr>
<tr>
<td>Miller et al9</td>
<td>Oral</td>
<td>308</td>
<td>No benefit</td>
</tr>
<tr>
<td>Matthy et al9</td>
<td>Intratumoral</td>
<td>88</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

Although levamisole, another "classic" immunostimulant, is now used routinely for colorectal cancer, its role in therapy for NSCLC remains unclear. The results of numerous trials (Table 2)10-18 in which levamisole was used as an adjuvant to surgery,10-15 radiotherapy,16,17 or chemotherapy18 were contradictory. Two studies10,15 demonstrated a trend toward improved survival and another12 demonstrated an increased recurrence-free survival in the levamisole-treated group in comparison to surgery alone. Results from all other trials11,14,16-18 were negative. Indeed, two large randomized trials11,17 showed decreased survival with levamisole; one of these11 was terminated early because of excessive noncancer deaths in the levamisole-treated group. No significant benefit was observed in adjuvant studies in which levamisole was

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combined with other biological agents, such as BCG, Corynebacterium parvum, or radiation and BCG.

In more recent studies, recombinant interleukin 2 (IL-2), the lymphokine found to produce encouraging remissions in human melanoma and renal cell carcinoma, was used. However, the administration of this agent for advanced NSCLC, either alone or in conjunction with immune cells, other cytokines, or hormones, has been marginally effective. In most IL-2-based phase II trials (Table 3), only occasional responses were recorded. Administration of high-dose IL-2 may increase capillary permeability, which causes excessive toxic reactions in several organ systems.

IFNs are the cytokines most frequently tested in cancer patients. There are currently three major types of IFN: α-IFN, β-IFN, and γ-IFN. These agents have proved to be effective in certain hematologic malignancies and in a few solid tumors. Their activity in NSCLC, however, seems to be marginal. The results of single-agent phase II studies using different types of IFN have been negative. Moreover, IFNs produced a variety of side effects, particularly at first exposure.

IFNs may potentiate the activity of cisplatin against NSCLC. The results of phase II studies combining these two agents in patients with advanced NSCLC were encouraging, but in phase III studies, IFN offered no survival benefit over chemotherapy alone.

Another avenue of investigation included the testing of IFNs as potential radiosensitizers. Phase I studies with α-IFN and γ-IFN demonstrated a significant increase of radiation pneumonitis that precluded further clinical testing. However, high response rate and no increased pulmonary toxic reactions were noted in a phase I/II study testing β-IFN. This type of IFN can therefore be considered in further studies of chest irradiation.

A few studies have used other active nonspecific immunotherapies. In a study by Dimitrov et al., patients with advanced NSCLC were randomized to chemotherapy with doxorubicin or the same chemotherapy combined with C parvum vaccine. A trend toward improved survival (p<0.07) was noted in the latter group. In one adjuvant trial of 309 patients with inoperable lung cancer (including 97 with small cell lung cancer), no benefit was demonstrated with intrapleural injections of Nocardia rubra cell wall skeletons. In a study of only four patients treated with mixed bacterial vaccines, one showed a partial response. Finally, in one randomized trial including 63 patients, a trend toward improved survival (p=0.08) was shown with the postoperative use of transfer factor, a dialyzable lymphocytic extract.

**ACTIVE SPECIFIC IMMUNOTHERAPY**

Active specific immunotherapy involves immune stimulation with allogeneic tumor extracts, inactivated tumor cells, or tumor antigens. There have been only a few trials testing these approaches (Table 5), usually small or suffering from serious methodologic flaws precluding conclusive analysis. Some investigators claimed a benefit with active immunization, but to our knowledge, these results have never been reproduced in larger studies. Such trials are difficult to perform owing to problems in obtaining immunogenic vaccine, especially from autologous material. In most instances, the patient’s own tumor is not available or is only weakly immunogenic.

Current experience of active specific therapy suggests that there is generally a marginal, if any, effect with this approach in NSCLC. Hope for advance in this type of treatment lies in the continuation of molecular biology research. For example, it is possible that introducing therapeutic genes into tumor cells, ex vivo or in vivo, will render them more susceptible to

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Characteristics</th>
<th>No. of Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amery et al</td>
<td>Levamisole administered preoperatively and postoperatively</td>
<td>211</td>
<td>Trend toward improved survival</td>
</tr>
<tr>
<td>Anthony et al</td>
<td>As above</td>
<td>318</td>
<td>Significantly poorer survival</td>
</tr>
<tr>
<td>Study Group for Bronchogenic Carcinoma</td>
<td>As above</td>
<td>111</td>
<td>Trend toward improved recurrence-free survival</td>
</tr>
<tr>
<td>Wright et al</td>
<td>Intrapleural BCG±levamisole</td>
<td>100</td>
<td>No benefit with levamisole</td>
</tr>
<tr>
<td>Herskovic et al</td>
<td>Postoperative irradiation±levamisole</td>
<td>74</td>
<td>No benefit with levamisole</td>
</tr>
<tr>
<td>Fox et al</td>
<td>Levamisole with C parvum</td>
<td>38</td>
<td>Trend toward improved survival with immunotherapy</td>
</tr>
<tr>
<td>Pines</td>
<td>Inoperable squamous cell lung cancer; BCG and levamisole therapy after radiotherapy</td>
<td>50</td>
<td>No benefit with immunotherapy</td>
</tr>
<tr>
<td>Perez et al</td>
<td>Inoperable NSCLC; radiation±levamisole</td>
<td>227</td>
<td>Decreased survival with levamisole</td>
</tr>
<tr>
<td>Davis et al</td>
<td>Advanced NSCLC; chemotherapy±levamisole</td>
<td>381</td>
<td>No benefit with levamisole</td>
</tr>
</tbody>
</table>
immune recognition. Clinical trials using these approaches have been initiated only recently in NSCLC and no success has been documented so far.

ADOPTIVE IMMUNOTHERAPY

T cells, macrophages, natural killer cells, and lymphokine-activated killer (LAK) cells as well as tumor-infiltrating leukocytes (TIL) can be used in adoptive immunotherapy. This therapy became feasible only when the isolation of cytokines enabled immune cells to be obtained ex vivo in adequate quantities. In the few studies so far, adoptive immunotherapy has been given alone or, more frequently, combined with IL-2. Clinical experience with this approach is scarce and does not allow any meaningful conclusion to be drawn.

PASSIVE IMMUNOTHERAPY

Passive immunotherapy involves the administration of specific antibodies directed against tumor-specific antigens. Early attempts used antisera to human cancers raised in dogs, horses, and goats. Recently developed murine monoclonal antibody (MoAb) technology has made it possible to obtain large quantities of antibodies with specific reactivity to human tumor-associated antigens. The MoAbs can be used in cancer therapy alone or as carriers of other substances (isotopes, immunotoxins, cytostatic agents, or biological agents). This approach appears particularly attractive because cytotoxic substances can be delivered directly to the tumor sites. MoAbs, conjugated with radiolabels, have potential use for diagnostic purposes, but therapeutic attempts in NSCLC have been disappointing.

Recently it has been shown that specific host antitumor responses can be raised using human anti-idiotypic (Ab-2) MoAbs. Anti-idiotypic antibodies are produced by humans after exposure to murine MoAbs (Ab-1) reacting with a tumor-associated antigen. Immunization of the host with Ab-2 in turn induces an anti-idiotypic response and production of anti-anti-idiotypic antibody (Ab-3). The latter has a binding region that can be the mirror image of the originally injected murine Ab-1, i.e., the two molecules have the same antigenic target. As a result, Ab-3 could react with the desired tumor antigen with the same reactivity as Ab-1, but it would be a human antibody produced endogenously. The final effect with this approach resembles that achieved with tumor antigen vaccines, but the idiotypic MoAb may be more immunogenic. Clinical trials with Ab-2 in patients with advanced colorectal cancer have shown good tolerance of this approach and promising clinical outcome. As lung and colon carcinoma share the same epithelial glycoprotein antigens, there is a sound basis for testing this method in NSCLC.

Another novel therapeutic method is the use of MoAbs directed against the epidermal growth factor receptor. This receptor is overexpressed in many cases of NSCLC, but is also distributed in normal tissue; its suitability as the immunotherapeutic target is therefore limited. Recently identified epidermal growth factor receptor mutants expressed in NSCLC and unique to malignant cells may provide a more specific target for immunotherapeutic intervention.

There are currently many factors limiting the clinical usefulness of MoAbs as therapeutic agents. First, most tumors are heterogeneous and in fact there are no truly tumor-specific antigens. Second, cytotoxic action of MoAbs may be reduced owing to poor access and penetration of the tumor by immunoglobulin molecules and to inhibition of antibodies by soluble tumor antigens. Finally, prolonged application of murine MoAbs may induce the development of human antimouse antibodies. Future research should be directed toward production of appropriate antibodies and development of more effective delivery systems.

### Table 3—Results of IL-2-Based Phase I/II Trials in the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Source</th>
<th>Agents Used</th>
<th>No. of Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al</td>
<td>IL-2 alone</td>
<td>1 NR</td>
<td></td>
</tr>
<tr>
<td>Yang et al</td>
<td>IL-2/LAK</td>
<td>5 N</td>
<td></td>
</tr>
<tr>
<td>Bernstein et al</td>
<td>IL-2/α-IFN</td>
<td>1 NR</td>
<td></td>
</tr>
<tr>
<td>Kradin et al</td>
<td>IL-2/TIL</td>
<td>11 NR</td>
<td></td>
</tr>
<tr>
<td>Scudeletti et al</td>
<td>IL-2 intralesional and systemic infusion</td>
<td>8 2 PR</td>
<td></td>
</tr>
<tr>
<td>Jansen et al</td>
<td>IL-2/α-IFN</td>
<td>11 N</td>
<td></td>
</tr>
<tr>
<td>Lisoni et al</td>
<td>IL-2/melanotin</td>
<td>9   2 PR</td>
<td></td>
</tr>
</tbody>
</table>

*TNF=tumor necrosis factor; NR=no response; PR=partial response.

### Table 4—Results of Phase II IFN Trials in the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Source</th>
<th>Agents Used</th>
<th>No. of Patients</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarna and Figlin</td>
<td>hIFN (Le)</td>
<td>38 1 PR</td>
<td></td>
</tr>
<tr>
<td>Leavitt et al</td>
<td>rα-IFN</td>
<td>8   NR</td>
<td></td>
</tr>
<tr>
<td>Olesen et al</td>
<td>rα-IFN</td>
<td>13 1 PR</td>
<td></td>
</tr>
<tr>
<td>Figlin and Sarna</td>
<td>rα-IFN</td>
<td>13 N</td>
<td></td>
</tr>
<tr>
<td>Grunberg et al</td>
<td>rα-IFN</td>
<td>19 N</td>
<td></td>
</tr>
<tr>
<td>van Zaandijk et al</td>
<td>hIFN (Le) or rα-IFN</td>
<td>10 NR</td>
<td></td>
</tr>
<tr>
<td>Rinaldi et al</td>
<td>rα-IFN+retinoic acid</td>
<td>21 1 PR</td>
<td></td>
</tr>
</tbody>
</table>

*hIFN (Le)=human interferon leukocyte-type; rα-IFN=recombinant α-interferon; NR=no response; PR=partial response.
Problems in Evaluating the Efficacy of Biological Agents

When interpreting the results of studies on biological approaches to the treatment of NSCLC, it is difficult to know whether the outcomes are actually poor or whether the methods of testing need to be improved to give a realistic result. Problems stem from inadequate phase I/II studies and small or inconclusive phase III trials. Optimal biological agents, doses, and schedules have been poorly defined by phase I/II studies, and it has not been possible to transfer the results directly to phase III clinical trials. In addition, there is no definitive dose dependency and the best route of administration in most instances has not yet been ascertained. Phase III studies with biological agents have traditionally been small because of technical difficulties, and the results consequently have been inconclusive. Heterogeneity of the studies has made meta-analysis unfeasible.

In vitro models, which have proved satisfactory in the initial testing of cytotoxic drugs and in radiation research, may be unreliable in indicating the potential benefits of biological therapeutic agents in the treatment of human malignancies. Classic animal models (eg, xenograft tests) have failed because they are immune-deficient systems in which a human tumor is combined with a rodent cytokine response. Early testing with these models can lead to clinical trials being started earlier than is ideal and to them being abandoned because of high toxic reactions or other factors.

In future clinical studies, the efficacy of biological agents can be clarified only if improved models are used. It is doubtful that classic immunostimulants, such as BCG or levamisole, will provide any benefit in NSCLC, so further investigations of these agents should not be made. Better patient and drug selection, realistic study design, and a strong commitment to completing the trial are critical factors. In addition, these investigations should encompass quality-of-life analysis and evaluation of the economic aspects of treatment.

Conclusions

At present, biological agents are marginally effective when used alone or in an adjuvant setting for the treatment of NSCLC. Future hopes for these therapies lie in ongoing biotechnologic research, more effective drug delivery, and better clinical testing.

References


Chang AYC, Keng PC. Potentiation of radiation cytotoxicity by recombinant interferons, a phenomenon associated with increased blockage at the G2-M phase of the cell cycle. Cancer Res 1987; 47:4338-41


Adverse drug reaction of gamma interferon [NSC #600662, ND 2192] reported to Cancer Therapy Evaluation Program. Bethesda, Md: National Cancer Institute, 1992; ADR Nos. 920151 and 927-872


