Report of a Clinical Trial in 12 Patients With Head and Neck Cancer Treated Intratumorally and Peritumorally With Multikine

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Background: There is cumulative evidence suggesting that cells of the immune system recognize and may participate in eradicating neoplastic cells. As a result, immune modulation, first with interleukin 2 and later with other cytokines, has been tried in the clinical setting as part of antitumor therapy.

Objective: To examine the effectiveness and toxicity of a combination of natural interleukins in patients with squamous cell head and neck cancer.

Methods: Twelve previously untreated patients with various head and neck cancers were treated by peritumoral injection of a combination of cytokines (Multikine), in addition to zinc sulfate, indomethacin, and a single dose of cyclophosphamide, which were administered systemically. Response was evaluated clinically and histopathologically. T-lymphocyte determinants were studied by fluorescence-activated cell sorter analysis (against controls).

Results: Two patients showed complete regression and another 2 showed partial regression. There were no serious adverse effects of treatment. Pathological study results showed tumor fragmentation and the appearance of multinucleated macrophages. Fluorescence-activated cell sorter analysis showed lymphocyte activation, reflected by an unusually high number of cytotoxic T-lymphocyte activation 4 cells and natural killer cells.

Conclusion: Multikine warrants further investigation for inclusion in the pharmacotherapeutic armamentarium of head and neck cancer.


THERE IS increasing evidence that patients with head and neck cancer have immunodepression and may, therefore, benefit from immune-enhancing treatment in terms of tumor containment and prognosis.1,3 In 1993, Katz² was the first to suggest that head and neck cancers arise in the presence of underlying cellular immune deficiency. This assumption was later supported by the studies of Clark4 and Hadden.5,6 The specific defects in cellular immune functions reported in this patient population include altered effectiveness of tumor-infiltrating leukocytes, such as T lymphocytes and natural killer (NK) cells,7,8 decrease in T-lymphocyte number, macrophage and monocyte dysfunction, and anergy.10 Some researchers11 have implicated general immunosuppression and local immunosuppressive factors derived from the tumor itself in the immune-compromised state.

Interleukins (ILs), through activation of the failing immune system, are effective in the treatment of malignant melanoma and renal cell carcinoma, leading to regression of lung metastases and improved disease-free periods.9,12 The source of the ILs may make a difference, with naturally produced ILs apparently being more effective than recombinant ones.7 Adverse effects and toxicity vary by mode of administration. The intravenous route is accompanied by a flulike feeling and fever, whereas peritumoral injection is associated with fewer adverse effects.13 The safety of the intrallesional administration of ILs from lymphoblastoid lines was demonstrated as early as 1976 by Papermaster et al,14 and later confirmed by Hadden2 and others.15 Interleukin 2 has been reported to induce CD56 lymphocyte proliferation and activation.16 Administered in a continuous-mode infusion, IL-2 selectively expands the absolute number of human NK cells in vivo after 4 to 6 weeks of therapy.17 Interleukin 12 plays a critical role in modulating the activities of NK cells and T lymphocytes. In animal models, IL-12 has antitumor effects that are likely mediated by its ability to enhance the cytotoxic activ-
ies,20,21 endolymphatic administration of ILs caused an complete regression of 2 lip cancers after local injections of recombinant IL-2. Hadden5,6 reported tumor regression and the metastatic process.20,21

Regarding head and neck cancer, the effect of immune-enhancing treatment has been investigated in only a few patients. Cortesina et al21 suggested that temporary regression of recurrent head and neck tumors may result in an increase in host resistance against tumor cells and the metastatic process.20,21

As follows: older than 18 years, histological diagnosis of squamous cell carcinoma on surgical or fine-needle aspiration biopsy specimen, and an expected survival of at least 6 months.

Patients who were pregnant, had received radiation to the same site, or had a gastric or duodenal ulcer were excluded. Patients proved anergic by a skin test result were also excluded because we assumed they lacked the potential to respond to immune stimulation by Multikine, and patients allergic to ciprofloxacin were excluded because the Multikine solution contains ciprofloxin as a protection against bacterial contamination. All participants signed an informed consent form in accordance with the recommendations of the Declaration of Helsinki (1985). The study was approved by the Rabin Medical Center Review Board.

PATIENT EXAMINATION

General assessment before treatment included obtaining a medical history, performing a physical examination and a hematological and blood chemistry workup, electrocardiography, chest cardiography, and obtaining a computed tomographic scan of the head and neck. A picture of the tumor was also taken, when possible. Tumor size was determined by measuring the 2 major perpendicular diameters. The patients were interviewed daily and asked about the degree of tongue mobility and pain.

TREATMENT

A Multikine solution (Cel Sci Corporation) was injected peri-tumorally (patients 1-11) or perilymphatically (patient 12) for 10 days. The manufacturer lists the following components in the Multikine solution: IL-2, IL-1α, IL-1β, granulocyte-macrophage colony-stimulating factor, interferon α, tumor necrosis factor α, tumor necrosis factor β, IL-3, IL-4, IL-6, IL-8, IL-10, macrophage inflammatory protein 1α, and granulocyte colony-stimulating factor. For the peritumoral approach, the total quantity of 2 or 4 mL was divided into 4 equal parts and injected at 4 equidistant points along the periphery of the tumor to a depth of 5 mm. For the perilymphatic approach, the total quantity of 4 mL was divided and injected at 4 arbitrary points at the periphery of the mastoid tip adjacent to the jugulo-gastric nodes. Ten patients (patients 1-10) received 800 U, and 2 (patients 11-12) received 1600 U, at a concentration of

Table 1. Clinical Data of the 12 Study Patients*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Site of the Primary Tumor</th>
<th>Grade</th>
<th>Dose, mL</th>
<th>Clinical Response†</th>
<th>Outcome</th>
<th>Follow-up, mo</th>
</tr>
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<tbody>
<tr>
<td>1/F/61</td>
<td>Hard palate</td>
<td>Mod</td>
<td>2</td>
<td>None</td>
<td>AWD</td>
<td>12</td>
</tr>
<tr>
<td>2/M/73</td>
<td>Tongue</td>
<td>Mod</td>
<td>2</td>
<td>Partial</td>
<td>AWD</td>
<td>28</td>
</tr>
<tr>
<td>3/M/82</td>
<td>Hard palate</td>
<td>Well</td>
<td>2</td>
<td>None</td>
<td>AND</td>
<td>26</td>
</tr>
<tr>
<td>4/M/69</td>
<td>Retromolar triangle</td>
<td>Mod</td>
<td>2</td>
<td>Complete†</td>
<td>Dead</td>
<td>24</td>
</tr>
<tr>
<td>5/F/77</td>
<td>Tongue</td>
<td>Mod</td>
<td>2</td>
<td>None</td>
<td>Dead</td>
<td>7</td>
</tr>
<tr>
<td>6/M/73</td>
<td>Lip</td>
<td>Well</td>
<td>2</td>
<td>None</td>
<td>AND</td>
<td>24</td>
</tr>
<tr>
<td>7/F/43</td>
<td>Tongue</td>
<td>Mod</td>
<td>2</td>
<td>Partial</td>
<td>AND</td>
<td>20</td>
</tr>
<tr>
<td>8/M/78</td>
<td>Skin</td>
<td>Mod</td>
<td>2</td>
<td>None</td>
<td>AWD</td>
<td>18</td>
</tr>
<tr>
<td>9/F/89</td>
<td>Skin</td>
<td>Mod</td>
<td>2</td>
<td>None</td>
<td>AND</td>
<td>18</td>
</tr>
<tr>
<td>10/M/81</td>
<td>Retromolar triangle</td>
<td>Mod</td>
<td>2</td>
<td>None§</td>
<td>AND</td>
<td>18</td>
</tr>
<tr>
<td>11/M/79</td>
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<td>Well</td>
<td>4</td>
<td>Partial</td>
<td>AND</td>
<td>16</td>
</tr>
<tr>
<td>12/M/82</td>
<td>Unknown</td>
<td>NA</td>
<td>4</td>
<td>Complete</td>
<td>AND</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: AND, alive with no evidence of disease; AWD, alive with disease; Mod, moderately differentiated squamous cell carcinoma; NA, data not applicable; Well, well-differentiated squamous cell carcinoma.

*All patients had a T2 N0 M0 tumor, except for patient 5 (who had a T2 N0 M1 tumor).
†See the “Postoperative Clinical Assessment” subsection of the “Methods” section for a description of the clinical responses.
§This patient developed Wegener granulomatosis.
¶This patient had a second primary tumor in the oral cavity.

METHODS

PATIENTS

Twelve patients with previously untreated head and neck carcinomas were included in this clinical trial. The primary site of the lesions is presented in Table 1. Inclusion criteria were as follows: older than 18 years, histological diagnosis of squamous cell carcinoma on surgical or fine-needle aspiration biopsy specimen, and an expected survival of at least 6 months.
400 U/mL. (According to protocol stipulation, the first 10 patients to participate in the study received a total dosage of 800 U, whereas the next 10 were designed to receive 1600 U in an attempt to evaluate the effect of dose on tumor regression.) The treatment protocol also included the following: intravenous cyclophosphamide in a single low dose of 50 mg/m² to reduce suppressor T-lymphocyte activity; intraoral indomethacin, 75 mg, from day 1 to day 21, to decrease levels of prostaglandin, which mediates macrophage-induced immune suppression; and oral zinc, 142 mg, from day 1 to day 21, to augment T-suppressor T-lymphocyte activity; intraoral indomethacin, 75 mg, from day 1 to day 21, to decrease levels of prostaglandin, which mediates macrophage-induced immune suppression.

**POSTOPERATIVE CLINICAL ASSESSMENT**

Patient response was categorized as follows: complete regression, complete tumor regression documented clinically and histologically; partial regression, tumor shrinkage of at least 50% of its original size according to the physician's examination; and no response, tumor shrinkage of less than 50% of its original size according to the physician's examination; and no response, tumor shrinkage of less than 50% of its original size according to the physician's examination; and no response, tumor shrinkage of less than 50% of its original size according to the physician's examination; and no response, tumor shrinkage of less than 50% of its original size according to the physician's examination. Tongue mobility and patient well-being were also documented. All adverse reactions during the study were recorded. Blood count and levels of electrolytes and enzymes were evaluated before and after Multikine treatment.

**HISTOPATHOLOGICAL ASSESSMENT**

In 11 patients, the diagnosis was based on the results of a surgical biopsy of the primary tumor, and in 1 patient (with a neck node metastasis of unknown origin), on the results of fine-needle aspiration biopsy and quadroscopy. Posttreatment samples were available for histopathological analysis in 10 patients. Sections (4-µm thick) from the paraffin-embedded specimens were stained with hematoxylin-eosin. The tumors were graded according to the degree of differentiation (well differentiated, moderately differentiated, and poorly differentiated). Lymphocytes, macrophages (mononucleated and multinucleated), plasma cells, granulocytes, and eosinophils were graded as follows: 0, no infiltration; 1, low infiltration; 2, moderate infiltration; and 3, heavy infiltration. Special note was taken of the extension of inflammatory cells into the tumor. Tumor necrosis and fragmentation, stromal edema, and stromal fibrosis were graded from 0 to 3 (0, absent; 1, mild; 2, moderate; 3, prominent). Tumor regression was recorded as absent or present. We also attempted to evaluate the degree of regression based on the presence of keratin remnants (Table 2).

**FLOW CYTOMETRY ANALYSIS**

Of the 12 patients, 8 were studied for various T-lymphocyte determinants by fluorescence-activated cell sorter (FACS) analysis. Human peripheral blood mononuclear cells were obtained by density centrifugation (Ficoll-Hypaque method) and washed and suspended in phosphate-buffered saline. Aliquots of 0.5 × 10⁶ cells per test tube were used. The cells were incubated with the following monoclonal antibodies: CD3, CD4, CD8, CD56, CD28, cytotoxic T-lymphocyte activation 4 (CTLA-4), CD25, and Burkitt lymphoma cell membrane activated T cells (BAT: Pharmingen, San Diego, Calif) for 30 minutes at 4°C. After washing and centrifugation for 5 minutes at 1200 rpm with phosphate-buffered saline, paraformaldehyde was added for fixation. Cell labeling was performed by incubation with anti–mouse fluorescein isothiocyanate (Jackson, Immuno-Keywords Labs, Palo Alto, Calif). Mouse anti–human IgG or anti–mouse fluorescein isothiocyanate was used as an isotope control for the monoclonal antibodies. Cells were analyzed by FACS analysis (FACScan; Becton Dickinson Microbiology Systems, Cockeysville, Md). The results of FACS analysis of 6 patients with head and neck cancer who had not received Mul-
tikine treatment served as the control. All patients were followed up monthly and examined for tumor recurrence and performance. The follow-up varied between 4 months and 3 years.

RESULTS

CLINICAL RESULTS

Of the 12 patients, 9 had a primary lesion in the oral cavity and 2 had skin cancers (squamous cell carcinoma) of the head and neck area. One patient was treated for a neck metastasis of unknown origin. Ten patients underwent surgical treatment after Multikine injection, and 2 (patients 1 and 5) refused surgery and underwent a biopsy only.

Of the latter 2 patients, patient 1, who underwent partial reduction of a palatal tumor by laser, is alive at 30 months after the Multikine regimen, with persistent disease confined to the hard palate. Patient 5, who had tongue cancer, showed a reduction in tumor size in response to Multikine, but was unable to be located for follow-up and died 7 months later of unknown causes.

The other 7 patients with oral cavity tumors showed various degrees of response to treatment. One patient (patient 4) had complete tumor regression clinically and histologically, and 2 patients (patients 2 and 11) had a partial response clinically and pathologically. Additional responses noted by the treating physician (R.S.) and reported by another 4 patients after Multikine treatment included flattening of the tumor, increased mobility of the tongue, and a reduction in pain. Patient 4, whose primary tumor completely regressed, also had a neck node metastasis that did not respond to peritumoral Multikine injections; this was treated with neck dissection followed by radiation. The patient died 12 months later of sepsis associated with marked cervical and bilateral parotid enlargement. Biopsy specimens obtained from one of the parotid glands and from a lymph node diagnosed the patient as having a granulomatous disease. There was no evidence of recurrence of the primary tumor or of neck metastases at death. Patient 6 (Figure 1) underwent surgical removal of a lip tumor, and although 2 margins were microscopically involved, he refused additional surgery or radiation. At present, 24 months postoperatively, there is no evidence of tumor recurrence or persistence. The 2 patients with skin cancer (patients 8 and 9) failed to show a significant response to treatment. Patient 12, with a neck metastasis of unknown origin, was treated by a perinodal injection of Multikine. He showed complete tumor regression clinically and histologically, and major regression on a computed tomographic scan (Figure 2). The patient underwent a neck dissection. A histopathological analysis showed replacement of the metastasis by fibrosis. One patient (patient 10) had a second primary tumor in the palate 1 year after initial treatment. He received radiotherapy as definitive treatment, and is healthy, with no evidence of disease in either site. Overall, of the 12 patients in the study group, 10 are alive, 1 with persistent disease and 1 after treatment for a second primary tumor (this patient is healthy). One of the patients who died had no evidence of tumor at death (but had cervical lymphadenopathy, consistent with a granulomatous disease). There are no details available concerning the state of disease in the second patient participating in the study who died, because he was unable to be located for follow-up.

LABORATORY RESULTS

There were no obvious effects of the protocol on routine laboratory variables (electrolyte levels, liver function, and hemoglobin level) either during or after treatment. There was, however, an elevation in total white blood cell count, from a mean of 7.43 x 10^3/µL before treatment to 8.97 x 10^3/µL after treatment. This difference was statistically significant (P < .05, χ^2 test). One patient with type 2 diabetes mellitus showed a decrease in fasting blood glucose levels, from a mean of 245 to 100 mg/dl (13.6-5.5 mmol/L).

HISTOPATHOLOGICAL RESULTS

Biopsy samples of 9 patients were analyzed before and after treatment (the 2 skin lesions were excluded). The patient with a neck metastasis of unknown primary origin was only partially evaluated. Four had well-differentiated carcinoma, and 6 had moderately differentiated carcinoma. Before treatment, fibrosis, necrosis, and stromal edema were not prominent, but lymphocytic infiltrates to various extents were present in all patients (Table 2 and Figure 3A). The infiltrates were found mainly in the stroma, and only focal infiltration into the tumor itself was noted. After treatment, 2 patients (patients 4 and 12) showed complete regression, 2 (patients 2 and 11) showed
partial regression, and 1 (patient 3) had a clear focus of regression. (In patient 4, the primary tumor regressed, whereas in patient 12, the neck metastasis disappeared.) An increase in the degree of lymphocytic infiltration was noted in 5 patients (Table 2 and Figure 3). The infiltrate also contained plasma cells, neutrophils, and eosinophils, as in the pretreatment specimens. Of special interest was the new posttreatment appearance of up to 5 multinucleated macrophages per high-power field in the patients with significant tumor regression (Figure 3B). The multinucleated macrophages were detected in 2 specific locations, namely, around the keratin debris and in the tumor-stroma interface (Figure 4), and they seemed to be actively engulfing the tumor cells. In 1 patient (patient 1), up to 3 multinucleated cells per high-power field were found in the pretreatment and posttreatment biopsy specimens. Although there was no evidence of major clinical tumor regression, this patient, who refused definitive surgery, remained healthy, without significant tumor growth throughout 30 months of follow-up. Stromal fibrosis, which was not present in any of the pretreatment biopsy specimens, was noted mainly in tumors showing regression, seeming to replace the tumors.

Figure 2. Computed tomographic (CT) scans of a neck metastasis from an unknown primary tumor. A, Before treatment. B, After treatment. There was tumor shrinkage. (A complete match between the 2 CT sections was not possible.) R indicates right side; L, left side.

Figure 3. Patient 3, who has carcinoma of the palate. A, A pretreatment biopsy specimen showing a well-differentiated squamous cell carcinoma with lymphocytic infiltrates in the stroma (arrows) (hematoxylin-eosin, original magnification ×100). B, A biopsy specimen after treatment with a mixture of interleukins (Multikine). Keratin pearls are shown, probably representing residual tumor. There are surrounding mononuclear and multinucleated macrophages (arrows) (hematoxylin-eosin, original magnification ×100).
A comparison of FACS analysis results of peripheral blood mononuclear cell samples from 6 patients with head and neck tumors who had not received Multikine treatment with patients after Multikine treatment reveals a dramatic change in the general appearance of the cell population (Figure 5). The post–Multikine treatment blood samples show a new distinctive population composed of highly scattered and granular cells, representing monocytes, macrophages, and neutrophils (Figure 5A). This population is nearly missing in the pretreatment group (Figure 5B).

Figure 6 summarizes the results obtained by FACS analysis of specific subpopulations in peripheral blood mononuclear cells from 8 of the patients treated by our protocol and compared with 6 patients with head and neck cancer who were not participating in our study (Figure 6). The T-lymphocyte (CD3-positive) count was maintained at a normal average rate of 65%, in contrast to the high count of NK cells (79% were CD56 positive) in the posttreatment blood samples, compared with controls (50%). The CD4/CD8 ratio was 1:1 (30% and 39%, respectively). CD28 and CTLA-4 are T-lymphocyte activation determinants. While a normal percentage of CD28-positive cells was found in the peripheral blood of all 8 patients, 6 of them exhibited an exceptionally high expression of CTLA-4, compared with controls (none had any positive CTLA-4 reading). Lymphocytes from 4 of the 8 patients had more than 90% IL-2 receptor-positive T lymphocytes (CD25).

TOXICITY

No significant toxic effect of the treatment was registered in any of the patients participating in the study during or after treatment. Two patients complained of minor adverse effects, namely, headaches and palpitations, but it was unclear if they were related to the Multikine treatment. It was also unclear whether the development of sepsis and Wegener granulomatosis in patient 4 was connected to the Multikine treatment.

COMMENT

Recent findings of a depressed lymphoproliferative response to mitogens, depressed IL-2 production, and a depressed cutaneous reaction to recall antigens in patients with head and neck cancer all point to the presence of a depressed immune status. Studies using mouse models have shown that injections of low doses of ILs at the tumor growth site or around the tumor-draining lymph nodes trigger nonreactive lymphocytes to inhibit the growth of otherwise lethal tumor challenges. However, to our knowledge, the effect of this treatment approach has not yet been investigated thoroughly in clinical trials. Head and neck squamous cell carcinoma is a logical choice for locoregional treatment, because the tumor is mainly localized, well vascularized, and surrounded by a rich net of lymphatic tissue. Furthermore, it can be easily visualized, making peritumoral injection feasible and assessment of tumor regression possible. The present clinical study examined the effect of peritumoral injection of Multikine (a mixture of ILs) together with additional immune modulators, namely, zinc, indomethacin, and cyclophosphamide, on head and neck cancers. The design of the present study precludes an examination of the exact contribution of each of the components of Multikine, although an investigation of the effect of cyclophosphamide monotherapy in patients with head and neck cancer is under way. The manufacturer of Multikine regards ILs combined with cyclophosphamide (a T-lymphocyte modifier) and indomethacin (a B-cell activator) as a single treatment with different facets that complement each other or accelerate each other's activities. Accordingly, in the present study, we evaluated these 3 medications together, as different arms of a single treatment modality.

EFFECT ON THE TUMOR

The tumors in our sample were not homogeneous, making it difficult for us to draw statistically sound conclusions. One patient with retromolar cavity cancer (pa-
Patient 4) had complete regression of the primary tumor by clinical and pathological criteria. Two other patients with oral cavity tongue cancers (patients 2 and 11) had a partial response by clinical and pathological criteria (50% of the tumor was replaced by fibrosis). The 2 patients with skin cancers showed no real response to treatment. The single patient with a neck metastasis of unknown origin (patient 12), treated by perilymphatic injection, also showed complete regression (ie, resolution of the metastatic neck node). Although the node was not palpable after Multikine treatment and before surgery, the patient underwent supraomohyoid neck dissection, and a subsequent histological analysis revealed a 1.5 × 1.5-cm node with multinucleated macrophages engulfing and eating keratin debris—evidence of the past presence of epithelial tumor cells.

To better understand the effect of Multikine on tumor behavior, the tumors were carefully inspected by an experienced pathologist (M.F.). Traditionally, head and neck tumors are not referred to as immunogenic, because they lack the heavy lymphocytic infiltration that is present in melanoma and renal cell carcinoma, the prototypes of the so-called immunogenic tumors. Nevertheless, most of the pretreatment biopsy specimens in our study showed evidence of lymphocytic infiltration (Table 2 and Figure 3A). Because alcohol consumption is not common in Israel, it

**Figure 5.** Fluorescence-activated cell sorter analysis of peripheral blood samples of patient 4. A, After treatment with a mixture of interleukins (Multikine), a concentrated population of scattered granular cells is seen. B, Pretreatment sample, in which the granular cells are missing. FSC-H indicates forward scatter height; SSC-H, side scatter height.

**Figure 6.** Fluorescence-activated cell sorter (FACS) analysis of peripheral blood. A, Six untreated patients with head and neck cancer. B, Eight patients treated with a mixture of interleukins (Multikine). CTLA-4 indicates cytotoxic T-lymphocyte activation 4.
is possible that our population with head and neck cancer is not subjected to the depressing effect alcohol has on the immune system. This may be the explanation for the lymphocytic infiltration in the pretreatment biopsy specimens. Based on our observation of accelerated tumor regression after Multikine treatment, we suggest that Multikine has the potential to activate peritumoral macrophages already present before treatment and, thereby, to facilitate tumor killing. The presence of multinucleated macrophages in most of the pretreatment, but not the pretreatment, biopsy samples supports this assumption. Further support is provided by the complete tumor regression in 2 patients and the regression of varying degrees in several other patients, all associated with the keratin debris being eaten by macrophages (Figure 5).

We propose that peritumoral injections of Multikine, besides affecting the primary tumor, may be absorbed by the abundant submucosal lymphatic system and transmitted into the circulation, possibly leading to a general systemic effect. This theory is in line with our FACS and peripheral blood analysis findings of an increase in white blood cells in the peripheral blood, a marked increase in NK cell count (79% were CD56 positive vs 50% of the controls) (Figure 6), and an unusually high number of CTLA-4 cells (which express a T-lymphocyte activation determinant) compared with the control group (Figure 6). While the increase in peripheral white blood cells may be attributable to inflammation secondary to the injection rather than to a direct Multikine effect, this is probably not enough to explain the dramatic effect on CTLA-4. The elevation of CTLA-4 is probably the result of Multikine treatment, suggesting that Multikine may possess antitumor potential.

In conclusion, the present study, using histological and peripheral blood analyses, indicates that the peritumoral and perilymphatic administration of Multikine, in combination with zinc, indomed, and cyclophosphamide, is relatively safe and has an effect on tumor regression, probably through the enlistment of macrophages and the activation of lymphocytes. Further studies are needed to substantiate these findings and to define the best dosage and mode of administration of Multikine in patients with head and neck cancer.

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