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CLINICAL ONCOLOGY ALERT

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Peptide-pulsed Peripheral Blood Mononuclear Cells plus IL-12 as a Melanoma Vaccine

ABSTRACT & COMMENTARY

Synopsis: *Peptides from MAGE-3 and MelanA that bind to HLA-A2 and stimulate in vitro T-cell responses have been identified. A phase 1 study of immunization with MAGE-3 or MelanA peptide-pulsed peripheral blood mononuclear cells (PBMCs) coadministered with various doses of recombinant human interleukin (IL)-12 was performed in HLA-A2+ melanoma patients to determine toxicity and T-cell responses of this immunization strategy. Specific CD8+ T-cell responses, low toxicity, and some limited antitumor activity following vaccination were reported. This immunization approach is clinically feasible and warrants additional clinical evaluation.*

Source: Gajewski T, et al. *Clin Cancer Res.* 2001; 7(3 Suppl):895s-901s.

The stimulation of selective recognition and destruction of melanoma cells by components of the immune system is a central goal of many melanoma treatment strategies.[1-3] Achieving this goal requires that melanomas express antigens that can elicit immune responses. In addition, the immune response specific for a melanoma antigen must be able to mediate a protective and/or therapeutic effect. Extensive in vitro cellular and molecular analyses have identified melanoma-associated antigens that can stimulate T-cell responses, and many clinical trials are now in progress to determine whether effective in vivo T-cell mediated antimelanoma activity can be obtained against these melanoma-associated antigens. These antigens include the products of nonmutated genes expressed in melanoma cells and in the testis, such as the MAGE antigens, as well as differentiation antigens such as MelanA that have differential expression on melanoma cells compared with normal tissue.[4] While the optimal strategy to vaccinate patients with these antigens remains unknown, the role of IL-12 has been suggested as an important cytokine for stimulation of antigen-specific immunity.[5]

This phase 1 study by Gajewski and colleagues evaluated HLA-A2+ melanoma patients to determine the toxicity and immunologic

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activity of vaccination with MAGE-3 or MelanA peptide-pulsed autologous PBMCs plus various doses of recombinant IL-12. Patients were required to have metastatic disease, a tumor biopsy demonstrating expression of either MAGE-3 or MelanA by RT-PCR, and no requirement for immunosuppressive medications. The vaccine was available by obtaining 100-150 mL of heparinized blood prior to treatment and isolating PBMCs by centrifugation over a density gradient. The PBMCs were incubated with either MelanA (27-35) peptide (AAGIGILTV; 50 µL) or MAGE-3 (271-279) peptide (FLWGPRALV; 20 µL) for 1 hour, followed by irradiation (2000 rads) of the pulsed cells (~ 108 total). The vaccine was administered as a subcutaneous (SC) injection, and IL-12 at the assigned dose level (0, 30, 100, or 300 ng/kg/dose) was injected SC adjacent to a vaccine site on days 1, 3, and 5 of each cycle. Cycles were repeated every 3 weeks, and disease status was assessed every 3 cycles. An aliquot of the PBMCs was obtained at the time of vaccine preparation to fractionate CD8+ and CD8- T-cell populations for cryopreservation and subsequent immunologic assays.

A total of 15 patients were enrolled into the study and received MAGE-3 (7 patients) or MelanA (8 patients) either alone (4 patients) or together with IL-12 (either 30, 100, or 300 ng/kg/dose; 3, 4, and 4 patients, respectively). The overall clinical outcome included 1 complete response, 1 partial response, 4 mixed responses, 1 stable disease, and 8 patients with progressive disease. Toxicity was minimal and consisted primarily of grade 1 fatigue and fever in the cohorts of patients receiving IL-12 dose levels of 0, 30, or 100 ng/kg/dose. Toxicity was more severe in the IL-12 dose level of 300 ng/kg/dose with all patients experiencing grade 2-3 fatigue or myelosuppression. Specific T-cell reactivity against the immunizing peptide (either MAGE-3 or MelanA) was assessed by measuring peptide-specific interferon-gamma production by purified CD8+ T-cells prior to each immunization and after the third treatment. Increases in interferon-gamma producing CD8+ T-cells were seen following vaccination in several patients: 1 receiving no IL-12; 3 receiving 30 ng/kg/dose; 3 receiving 100 ng/kg/dose; and 1 receiving 300 ng/kg/dose at each of the IL-12 dose levels. In 2 patients with progressively growing tumors following vaccination, biopsies of the growing tumors were analyzed and shown by RT-PCR to be negative for the antigen used in the vaccine. Gajewski et al concluded that vaccination with peptide-pulsed PBMCs plus IL-12 induces specific immunity and has clinical activity. The development of polyepitope vaccines was suggested for future evaluation.

COMMENT BY MARK R. ALBERTINI, MD

The use of defined antigen vaccines for melanoma immunotherapy offers several potential advantages over the use of melanoma cell vaccine approaches. A defined peptide or gene therapy vaccine would be specific and only contain the "relevant" antigen as a melanoma vaccine. Thus, additional "irrelevant" antigens that are present in intact melanoma cells would not be part of the vaccine. Potentially immunosuppressive cytokines produced by intact melanoma cells would likewise not be part of the vaccine. A defined vaccine preparation for a given patient, perhaps dependent on the HLA type of the patient, could also make this type of vaccine a practical option for melanoma patients. Several clinical studies have reported antitumor activity and/or T-cell immunity in melanoma patients receiving defined antigen vaccine approaches.[6,7] Thus, significant enthusiasm is present for the clinical testing of defined antigen approaches for melanoma patients.

The current report by Gajewski et al demonstrates the clinical feasibility of a vaccine strategy using peptide-pulsed autologous peripheral blood mononuclear cells plus IL-12. The demonstration of some clinical activity in this small phase 1 study is encouraging. While increases in peptide-specific T-cell responses were seen

Clinical Oncology Alert, ISSN 0886-7186, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Clinical Oncology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $37.
Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$269 per year (Student/Resident rate: $105).

Multiple Copies
1-9 additional copies: $197 each; 10 or more copies: $175 each.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Ershler is on the speaker's bureau for Wyeth-Ayerst and does research for Ortho Biotech. Dr. Roberts is a contractor for Eli Lilly and Agouron and is a consultant for Novartis Pharmaceuticals. Dr. Albertini does research for Powder Ject vaccines, Inc and Lexigen Pharmaceuticals. Drs. Kaplan, Kotz, and Morris report no consultant, stockholder, speaker's bureau, research, or other financial realtionships with companies having ties to this field of study.

in patients following immunization, the assay for peptide specific responses required an initial period of in vitro stimulation prior to the analysis for peptide-specific responses. Additional assays, such as assays for intracellular cytokine production, may allow for analysis for peptide-specific responses without requiring significant additional in vitro culture of the T-cells.[8] The magnitude of the T-cell stimulation with this approach will require further analysis with a greater number of patients being treated with a similar vaccine dose.

In conclusion, vaccination with peptide-pulsed PBMCs plus IL-12 induced peptide-specific T-cell responses in some melanoma patients. The dose of IL-12 required for this vaccine has low toxicity, and the peptide-pulsed PBMC vaccine can be easily prepared. Further testing in melanoma patients is needed to better define the activity of this approach. ❖

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Molecular Predictors of Survival After Adjuvant Chemotherapy for Colon Cancer

ABSTRACT & COMMENTARY

Synopsis: *Chromosomal analysis on tumor tissue was performed on 460 patients subjected to fluorouracil-based chemotherapy for stage II and III colon cancer. Two chromosomal abnormalities were associated with favorable outcomes after adjuvant chemotherapy. It was postulated that this may be a first step toward individualized cancer treatment based on chromosomal markers.*

Source: Watanabe T, et al. *N Engl J Med*. 2001;344: 1196-1206.

Molecular predictors of outcome in colon cancer may guide delivery of appropriate chemotherapy regimens but remain largely undefined. Watanabe and colleagues tested colon cancer specimens, removed from patients in 2 National Cancer Institute (NCI) Gastrointestinal Intergroup trials, for such prognostic markers.

Specimens were resected from 460 patients undergoing 1 of 5 fluorouracil-based chemotherapy regimens for stage III or high-risk stage II colon cancer. A panel of molecular markers with previously established prognostic value was defined and included in an accompanying glossary. The presence of microsatellite instability (MSI: insertions or deletions of nucleotides within repeated sequences of DNA) was assessed using 1 of 2 general processing methods, dependent upon control tissue availability. Loss of heterozygosity (LOH: deletion of part or all of an allele) was determined by polymerase chain reaction (PCR) amplification, and PCR interpretability ranged from 67-94%. Immunohistochemical analysis was used to identify p53 and p21 abnormalities.

After completion of the molecular analysis, these findings were related to patient data from the Eastern Cooperative Oncology Group Statistical Center.

Survival analysis for patients with stage II disease was performed separately and lacked statistical power to draw conclusions.

Among patients with stage III disease, LOH at 18q (the Deleted in Colon Cancer [DCC] gene) was a significant indicator of recurrence and death and remained a significantly poor prognostic factor after adjustment for multiple markers. Retention of 18q was associated with 69% 5-year survival, while allelic loss at this site was associated with 50% 5-year survival ($P = .005$).

Those patients whose tumors had high levels of MSI, traditionally a favorable prognostic marker, experienced a 5-year disease-free survival rate of 68%, compared to 56% in the microsatellite stable group ($P = .02$). However, a significant overall 5-year survival difference between these groups was not realized.

Mutation in the gene for type II receptor for TGF-b1 (TGF-b1 RII), 1 marker of MSI, had a greater association with favorable prognosis. Mutation at this site was associated with 79% disease-free 5-year survival, while no mutation was associated with 59% disease-free 5-year survival ($P = .002$). Overall 5-year survival rates were 74% and 50% for patients whose tumors had a TGF-b1 RII mutation compared to those whose tumors did not, respectively ($P = .06$).

Lastly, among those patients with high levels of MSI, mutation of TGF-b1 RII conferred additional favorable prognosis, with 5-year survival rate of 74% compared to 46% in those patients with high levels of MSI and no

mutation of TGF-b1 RII (P = .04).

Watanabe et al concluded that the specific molecular markers listed above could be used to predict survival in patients with stage III resected colon cancer after adjuvant fluorouracil-based chemotherapy regimens. They postulated that prospective molecular marker investigation may eventually assist in developing alternative regimens for patients whose tumors do not respond to fluorouracil.

COMMENT BY ARDEN MORRIS, MD

If the recent American Society of Clinical Oncology annual meeting was any indication, molecular markers in cancer treatment are capturing the imagination of not only researchers but clinical practitioners as well.[1] Understanding molecular markers can improve efficacy of treatment in 3 ways: 1) development of marker-specific therapies, such as tamoxifen for ER+ tumors or cetuximab, which prevents the stimulation of ongoing cell division by blocking the epidermal growth factor receptor on colon and other tumors; 2) enhancement of cell-mediated immunity by vaccines targeted against specific tumor markers; and 3) characterization of markers on tumors that may be susceptible or resistant to specific therapies, in order to better identify efficacious treatment strategies for individual tumors.

Watanabe et al have addressed this last method of using markers to identify patients likely to have a favorable outcome after adjuvant fluorouracil-based treatment for colon cancer. Their results point to 2 favorable prognostic markers for stage III disease: retention of 18q, and mutation of TGF-b1 RII in tumors with MSI. 18q is the site of a tumor suppressor gene, DCC, which behaves similarly to p53. When mutated or deleted, these gene products no longer provide regulation of cell growth.[2] MSI, for which TGF-b1 RII is one marker, is associated with decreased metastasis and better overall prognosis.[3]

Although NIH consensus recommendations for adjuvant treatment of stage III colon cancer have been established, some stage III tumors have demonstrated resistance to fluorouracil-based regimens.[4,5] Moreover, adjuvant treatment for stage II disease remains controversial. Identification of tumor markers that could predict the benefit of specific adjuvant regimens would have a clear value in current colon cancer treatment. Watanabe et al have provided a first step toward more individualized and, therefore, more efficacious treatment. Further steps within this current investigation might include examining tumor tissue from those ECOG-enrolled patients who did not receive fluorouracil, to identify whether these same markers are present and whether any association with survival can be documented. ❖

Dr. Morris is Robert Wood Johnson Clinical Scholar, University of Washington, Seattle, Wash.

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Treatment of Metastatic Renal Cell Carcinoma with High-Dose Bolus IL-2 in a Non-Intensive Care Unit

ABSTRACT & COMMENTARY

Synopsis: *Despite its well-recognized limitations, high-dose IL-2 remains a consideration for otherwise healthy patients with metastatic renal cell carcinoma who are minimally symptomatic. One limitation to making this treatment more available has been timely access to ICU beds. This report outlines a 7-year experience in giving this treatment in a non-ICU setting. However, regardless of the setting, a well-trained, experienced, and motivated staff is critical if the treatment is to be given safely.*

Source: Gitlitz BJ, et al. *Cancer J*. 2001;7:112-121.

While low-dose subcutaneous il-2 is frequently used for the treatment of metastatic renal cell carcinoma (mRCC), high-dose IL-2, as approved by the FDA, remains the standard by which other therapies are judged. However, its toxicity and the need for intensive care unit (ICU) support have limited widespread use of this regimen. Patients with poor performance status or impaired cardiopulmonary function are not candidates due to the high rate of treatment-related complications and mortality. Implementation of the treatment is also limited by access to ICU beds. Gitlitz and colleagues at UCLA report the results of 124 patients treated from July 1992 to October 1999 with the standard high-dose IL-2 regimen (each course con-

sisted of 2 cycles of 600,000 IU/kg q 8 hours IV bolus over 15 minutes for a maximum of 14 doses over a 5-day period separated by 10-14 days). Patients who tolerated the treatment regimen and did not develop progressive disease were treated again 4-6 weeks later with a second course. If reversible grade 3 toxicity occurred, injections were withheld until the toxicity decreased to grade 0 or 1. If grade 4 nonhematologic toxicity occurred, no further injections were administered for that cycle. Typical toxicities included fever, rash, and pruritus, nausea and vomiting, diarrhea, electrolyte imbalances, and hypotension. Management included standard medications used for these symptoms, electrolyte replacement therapies, and pressors. Standard response criteria were used to assess efficacy.

Of the 124 patients, 53 (42.7%) had a performance status of 0. The remaining 57.3% had a performance status of 1. All had normal cardiac and pulmonary function. Approximately three-fourths of the patients had undergone a nephrectomy, and almost all had not previously received treatment for metastatic disease. The number of IL-2 injections administered in the first course of treatment was comparable to that of regimens using ICU support that have been reported in the literature (median of 19 doses; range, 5-28).[1] Approximately half of the patients received a second course of treatment and received a median of 13 doses (range, 2-20). Patients who responded did not, on average, receive more IL-2 than those who did not have an objective tumor regression. The complete and partial antitumor response rates (5.6% and 8.9%) and median response duration (18 months) were also comparable to those reported in the literature for high-dose IL-2.[1,2] The response rates for patients with performance status of 0 and 1 were 17% and 13%, respectively. Three of 7 patients with complete remissions, and 6 of 11 patients with partial responses had not yet progressed at the time of the analysis.

Almost half of the patients developed hypotension requiring pressor support. Approximately one-fifth of the patients developed an arrhythmia, but only 2 patients (1.6%) had ventricular tachycardia or fibrillation. Hallucinations or other significant neurotoxicity occurred in 35% of patients. Elevations of the serum creatinine and bilirubin and thrombocytopenia were common but easily managed. However, despite the presence of a well-trained and experienced staff, 7% of patients required transfer to an ICU at some point in their treatment. There were no treatment-related deaths.

COMMENT BY MICHAEL J. HAWKINS, MD

The use of high-dose IL-2 remains problematic. While treatment-related mortality has decreased with greater experience, effective management of side effects to maximize the amount of IL-2 administered remains a daunting task. Patients must be carefully selected based upon cancer-related performance status and comorbid conditions. With experience, however, personnel who are well trained and capable of providing blood pressure support as needed can administer this aggressive regimen largely outside of an ICU. Nonetheless, most patients will not benefit from this treatment while experiencing severe, but reversible, morbidity. However, despite these sobering considerations, some patients will achieve durable and at times complete regressions of their metastatic disease. Since similar results have not yet been reported for other therapies in mRCC, high-dose IL-2 remains a consideration for otherwise healthy patients who are minimally symptomatic from their cancer. This report addresses 1 resource limitation to potentially make this treatment more readily available. Regardless of the venue in which high-dose IL-2 is administered, the importance of a dedicated and experienced staff cannot be underestimated. ❖

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Zoledronic Acid: Better Than Pamidronate?

ABSTRACT & COMMENTARY

Synopsis: *Zoledronic acid, a newly developed bisphosphonate, was used in patients with neoplastic bone disease at 3 different doses (0.4 mg, 2 mg, 4 mg) and each administered intravenously over 5 minutes. For comparative purposes, a fourth group received pamidronate at the standard dose of 90 mg over 2 hours. Patients were treated monthly for a total of 10 months. The results indicate that the 2-mg and 4-mg dose of zoledronic acid was at least as effective and safe as pamidronate in treatment of osteolytic metastases.*

Source: Berenson JR, et al. *Cancer*. 2001;91: 191-200.

Zoledronic acid is a new generation bisphosphonate that has demonstrated greater potency and a higher therapeutic ratio than other bisphosphonates in

preclinical and early clinical trials.[1] For example, in recent phase III trials, a single infusion of 4.0 mg was significantly more effective than a single 90 mg pamidronate infusion in treatment of hypercalcemia associated with malignancy (HCM).[2] In the current study, Berenson and colleagues report the results of a double-blind, randomized dose-response study in which myeloma or breast cancer patients with known osteolytic skeletal metastases were treated with 1 of 3 doses of zoledronic acid or 90 mg of pamidronate.

This research project, supported by Novartis (the manufacturer of both pamidronate and zoledronic acid), was carried out at several institutions and involved the investigation of 280 patients who were treated with 0.4, 2.0, or 4.0 mg of zoledronic acid or 90 mg of pamidronate. For most, this was in addition to their tumor-directed chemotherapy. The primary end point was the proportion of patients with skeletal disease progression to the point where radiation therapy was required during the 10-month study duration. The study was without a "no treatment" arm. Thus, an assumption was made that approximately 30% of untreated patients would require radiation during this period, as was the case in similarly designed prior clinical trials in which there were nonbisphosphonate-treated patients.[3] The study was powered in such a way that if any of the 4 selected treatments resulted in a reduction to approximately 15% requiring radiation, there would be enough enrolled patients to detect this difference.

Other outcome variables were also examined. These included the number and type of skeletal-related events (SREs) (eg, fracture, spinal cord compression, hypercalcemia), bone mineral density (BMD), ECOG performance status, pain score, and analgesic score.

Analysis of the trial outcomes revealed that zoledronic acid (at 2-mg and 4-mg doses, but not at the lowest dose of 0.4 mg) reduced the need for radiation similar to that of pamidronate. Furthermore, SREs including hypercalcemia and pathological fractures were reduced similarly in these groups. Bone resorption, as measured by the urinary excretion of N-telopeptides (NTX) were observed in all treatment groups (including the lowest dose of zoledronic acid), and this correlated with increased BMD in all groups. The decrease in NTX and the increase in BMD were observed to be dose-related for the zoledronic acid-treated patients (greater effects in those treated at 4 mg).

Although infusion-related skeletal pain was common in all groups (40-60%), significant adverse events were uncommon and there was no difference among the treatment groups. There was a notable rise in serum creatinine in some patients. Thirty-seven patients had an increase in serum creatinine of at least 0.5 mg/dL, and this seemed to be dose-related for the zoledronic acid treatment groups. However, only 5 patients had grade 3 creatinine elevations, and this occurred in 1 patient in each of the zoledronic acid groups and in 2 patients in the pamidronate group.

Thus, this study established that a 5-minute infusion of 2 mg or 4 mg of zoledronic acid was at least as effective and safe as a 2-hour 90-mg pamidronate infusion in treatment of osteolytic disease in breast cancer and myeloma.

COMMENT BY WILLIAM B. ERSHLER, MD

Zoledronic acid is being developed as a third-generation bisphosphonate for the treatment of cancer-related bone disease. Early studies have indicated that it is more potent and probably more effective than earlier drugs in this general class, including etidronate, alendronate, and pamidronate. Furthermore, because of the lower dose required, it can be safely administered over a much shorter period of time. This would offer significant practical advantages in the outpatient setting.

The current study was not designed to compare zoledronic acid with pamidronate, but to establish an effective dose range for its use in this setting. A larger, multiinstitutional study is currently underway to determine if zoledronic acid is indeed more effective.

The rise in serum creatinine is of some concern, inasmuch as it occurred in a dose-related manner. In other trials, an 8 mg dose of zoledronic acid has been used and it is possible that significant renal toxicity may be observed. Slowing the rate of infusion may be sufficient to reduce renal toxicity, but this remains to be established.

Patients with myeloma and with breast cancer are at risk for developing generalized osteoporosis in addition to lytic metastases. Thus, it was encouraging to see a fairly pronounced rise in BMD (6.2-9.6% for the 3 zoledronic acid groups) over the relatively short 10-month treatment period. This compares favorably to all forms of osteoporosis treatment, including the daily oral administration of alendronate, which over 3 years was shown to result in an increase in BMD by 8.8%.[4] It is possible that zoledronic acid, administered by periodic brief infusions, will offer therapeutic advantages over alendronate in the management of nonmalignancy-associated osteoporosis. This, no doubt, is under consideration by the developers of this exciting new agent. ❖

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Soluble IL-2 Receptor: A Prognostic Indicator in Head and Neck Cancer

ABSTRACT & COMMENTARY

Synopsis: *The TNM classification for head and neck squamous cell cancer is useful, but it is not adequate for determining patients at risk for local recurrence, distant metastases, and survival. In this report, evidence is presented that measurement of serum soluble interleukin-2 receptor, obtained at the time of diagnosis, is a useful predictor of the development of metastases and overall survival in patients with this tumor type.*

Source: Tartour E, et al. *Lancet*. 2001;357:1263-1264.

Tumor size, lymph node involvement, and the presence or absence of metastatic disease are useful prognostic indicators for head and neck squamous cell carcinoma (HNSCC), but additional indicators are needed to better predict which patients are likely to have aggressive disease and shorter survival. In an earlier study,[1] Tartour and colleagues were to establish an association of high levels of soluble IL-2 receptor (sIL-2-R) and poor survival in 85 patients with HNSCC. In the current report, 234 HNSCC patients were examined in a prospective, multivariate study.

The 234 patients included 112 with tumors in the oral cavity, 33 with tumors in the oropharynx, 41 with hypopharynx tumors, and 48 with tumors of the larynx. Measurement of sIL2R was by ELISA and patients were either considered normal (< 70 pmol/L) or high (> 70 pmol/L). The 70 pmol/L level was chosen because that represents the 95th percentile in healthy people.

High sIL-2-R levels at diagnosis of HNSCC were correlated with shorter survival. At 3 years, the overall survival was 64.4% in patients with sIL-2-R in the normal range compared to 29.8% for patients with high sIL-2-R levels. Multivariate analysis (including TNM classification, primary tumor site, performance status, C-reactive protein, IL-6 levels, and sIL-2-R), only 4 variables influenced overall survival probability: serum sIL-2-R concentrations ($P < .0001$), lymph node involvement at diagnosis ($P = .0015$), performance status ($P = .0001$), and tumor stage ($P = .0097$).

Local recurrence and metastatic-free survival were also examined. A trend toward an association between serum sIL-2-R and local recurrence was observed, but this did not reach statistical significance ($P = .081$). The greatest predictors of local recurrence were initial tumor size (T score) and lymph node involvement. However, serum sIL-2-R concentrations were highly correlated with metastatic-free survival. Only 11.5% of patients with initially normal sIL-2-R levels developed distant metastases during the 3 years, compared to 34% of patients with high levels. In multivariate analysis, this reached a high level of significance ($P = .0002$). Thus, Tartour and colleagues suggest that initial serum sIL-2-R is a useful predictor of aggressive disease in patients with head and neck squamous cell carcinoma.

COMMENT BY WILLIAM B. ERSHLER, MD

This is an interesting report that expands earlier, and less complete findings from the same group that elevated sIL-2-R serum levels obtained at the time of diagnosis correlated with the development of metastatic disease and shorter survival. Inasmuch as this is a reliable and inexpensive assay (ELISA), if this work is confirmed by other investigators, it may become a useful initial diagnostic adjunct, particularly when questions regarding the advisability of systemic chemotherapy or postoperative radiation therapy are under consideration. Patients with elevated levels might be shown in future research to benefit from more aggressive adjuvant therapy.

Additional future research might also address the suitability of this marker (sIL-2-R) for assessing the completeness of surgery, the response to radiation or chemotherapy, and the early detection of recurrent disease. Indeed, if this is the case, sIL-2-R determination will become a routing measure in the management of these cases. However, other conditions may also be associated with elevated levels of sIL-2-R, including chronic or acute infections, or other malignancies. Thus, the findings are early, albeit intriguing. Hopefully, within a few years we'll have the answers to these questions and possibly a new and useful tumor marker for head and neck cancer. ❖

Reference

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CME Questions

1. **In the treatment of patients with osteolytic neoplastic disease, zoledronic acid, when compared to pamidronate, has been shown to:**
   a. be superior in preventing fractures.
   b. require a much shorter injection (infusion) time.
   c. be superior in preventing hypercalcemia.
   d. All of the above

2. **Which of the following statements is true about peptide-pulsed peripheral blood mononuclear cells plus IL-12 as a melanoma vaccine?**
   a. The toxicity of IL-12 makes this approach difficult for patients.
   b. Extensive cell culture is required for the mononuclear cells needed for this vaccine.
   c. Specific CD8+ T-cell responses were seen following vaccination.
   d. Nonspecific immune activation was seen following vaccination.

3. **Which of the following is (are) the tumor suppressor gene(s)?**
   a. DCC
   b. p53
   c. Both
   d. Neither

4. **What percentage of patients treated with bolus high-dose IL-2 can be expected to develop hypotension that requires pressor support?**
   a. < 1%
   b. 5-10%
   c. 20-30%
   d. 40% or more

In Future Issues:

HRT After Diagnosis of Breast Cancer