Challenging the Gold Standard: Aromatase Inhibitors in Postmenopausal Women with Early Breast Cancer

IL-2, Vaccines, and Cell-Based Immunotherapy: What the Future Holds

Treatment Options for Hepatic Colorectal Metastases
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**Improving Outcomes: Aromatase Inhibitors vs. Tamoxifen in the Neoadjuvant Setting**

Breast cancer remains the second-leading cause of cancer death in women in the United States, making research in neoadjuvant and adjuvant therapies a priority in this disease. “While most neoadjuvant therapy for breast cancer involves chemotherapy, evidence suggests that endocrine therapy in this setting may also be effective in postmenopausal women with hormone receptor-positive breast cancer,” said Veronica Shim, MD, Kaiser Permanente Department of Surgery, Oakland, and Assistant Clinical Professor, University of California, San Francisco. Dr. Shim provided an overview of three clinical trials comparing tamoxifen with an aromatase inhibitor in the primary neoadjuvant treatment of this patient population.

### Neoadjuvant Treatment Goals and Options

According to Dr. Shim, the goals of neoadjuvant therapy are multiple (Table 1), and current neoadjuvant treatment options include chemotherapy or endocrine therapy with tamoxifen or an aromatase inhibitor. Good candidates for neoadjuvant endocrine therapy include the elderly with hormone receptor-positive, large breast cancer who are unable to tolerate chemotherapy and desire breast conservation. “Patients with cardiovascular comorbidity are particularly good candidates for aromatase inhibitor therapy, since tamoxifen is associated with increased rates of stroke and thromboembolic events,” Dr. Shim explained (Howell et al. *Lancet*. 2005;365(9453):60).

#### Neoadjuvant Endocrine Therapy: The Data

**P024 Trial**

In the P024 double-blind, randomized, multicenter phase IIb/III study, postmenopausal women with estrogen- or progesterone-positive disease who were not eligible for breast-conserving surgery underwent neoadjuvant therapy with either tamoxifen 20mg qd or letrozole 2.5mg qd for 4 months. “The results showed comparable safety profiles with tamoxifen and letrozole, and significantly superior objective treatment response rates in the letrozole group by clinical, ultrasound, and mammographic monitoring,” Dr. Shim reported. “Importantly, the rate of breast conservation was also significantly higher for women receiving letrozole,” she noted (Eiermann et al. *Ann Oncol*. 2001;12:1527).

**IMPACT Trial**

In the IMPACT study, women with hormone receptor-positive breast cancer were randomized to receive neoadjuvant therapy with either tamoxifen, anastrozole, or both for 3 months. The results showed no difference in response rates between the three treatment groups. “However, in those initially having tumor size > 2cm, significantly more patients who received anastrozole were able to undergo breast-conserving surgery rather than mastectomy,” Dr. Shim explained (Smith and Dowsett. *Breast Cancer Res Treat*. 2003;82(suppl 1):S6).

**PROACT Trial**

In the PROACT double-blind, randomized, multicenter phase III trial, postmenopausal women with hormone receptor-positive breast cancer received neoadjuvant therapy with either tamoxifen or anastrozole for 4 months. A subset of patients also received chemotherapy. In this study, the overall objective response rates were comparable; however, response rate was superior with anastrozole in patients who 1) had initially inoperable disease or 2) were initially deemed mastectomy candidates and received only endocrine therapy. (Cataliotti et al. *Eur J Cancer*. 2004;2(suppl):69).

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**Table 1. Neoadjuvant Treatment Goals**

- To decrease primary tumor burden and allow for possible breast-conserving surgery
- To determine tumor sensitivity/resistance to therapy
- To identify prognostic and predictive factors of response to treatment

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Endocrine Therapy and Tumor Characteristics

Analyzing the existing data by tumor characteristics may be key to identifying prognostic and predictive treatment response factors. The PO24 trial showed that letrozole was more effective than tamoxifen in tumors with lower estrogen expression. Another subset of patients that seem to be more responsive to aromatase inhibitors are patients with HER2-overexpressed tumors. Ellis and colleagues analyzed the PO24 trial data by response rate and HER2-positive disease. “This analysis showed that patients whose disease had high HER2 expression responded significantly better to letrozole than to tamoxifen,” Dr. Shim said (Ellis et al. J Clin Oncol. 2001;19:3808). Similarly, an analysis of HER2-positive tumors in the IMPACT trial showed significantly superior clinical response rates in those receiving anastrozole versus tamoxifen (Smith & Dowsett. Breast Cancer Res Treat. 2003;82(suppl 1):S6).

In a recent study, Murray and colleagues studied estrogen, progesterone, Ki67, and HER2 expression in postmenopausal patients with early breast cancer who received neoadjuvant therapy with either anastrozole or letrozole for 14 days. Post-treatment tumor samples showed that anastrozole and letrozole therapy significantly reduced estrogen and progesterone expression, as well as the proliferation marker Ki67. In addition, in tumors with low estrogen receptor expression (Allred 2-5), Ki67 was significantly lower in the letrozole-treated tumors (Update of Murray et al. Breast Cancer Res Treat. 2004;88 (suppl 1):S37).

In conclusion, Dr. Shim reported, “Overall, these preliminary data suggest that aromatase inhibitors are more effective than tamoxifen in increasing the breast conservation rate in postmenopausal patients with hormone-positive tumors. Also, aromatase inhibitors seem to be more effective than tamoxifen in tumors with low estrogen receptor expression or HER-2 overexpression.” Research is currently ongoing to identify biologic markers to help predict treatment response and prognosis in postmenopausal women undergoing neoadjuvant endocrine therapy for early breast cancer.

Appreciating the Continued Risk of Recurrence in Women with Early Breast Cancer

“T
de risk of breast cancer recurrence, even in early disease, remains substantial far beyond 5 years postdiagnosis, regardless of nodal status or tumor size,” said Terry P. Mamounas, MD, MPH, Associate Professor of Surgery, Northeastern Ohio Universities College of Medicine; Medical Director, Aultman Cancer Center, Canton, Ohio. According to Dr. Mamounas, adjuvant tamoxifen therapy substantially reduces the risk of breast cancer recurrence but offers no benefit with use beyond 5 years (Fisher et al. J Natl Cancer Inst. 2001;93:684). Dr. Mamounas provided an overview of prognostic indicators and risk of recurrence in early breast cancer.

Prognostic Factors

Common prognostic factors in early breast cancer include lymph node status, tumor size, histologic tumor grade, age, estrogen receptor (ER) status and HER2/neu status. Recently, gene expression profiling has been found to be effective in determining outcome in early-stage breast cancer. “While node-negative status is commonly associated with a favorable outcome, most risk assessments consider only the initial 5 years after diagnosis. The actual long-term risk of recurrence and death is not well understood,” Dr. Mamounas explained.

Long-Term Recurrence Risk

Several clinical trials indicate a need to address the significant rates of late recurrence in early breast cancer. In one retrospective analysis, Saphner and colleagues evaluated data from 3585 pre- and postmenopausal patients, 75% of whom were node-positive. The results of this analysis showed an appreciable risk for breast cancer recurrence for at least 12 years, with 60% of recurrences occurring more than 5 years post-surgery. “The risk for late recurrence is substantial for both node-positive and node-negative tumors, at an overall annual rate of 4.3%,” Dr. Mamounas said. Importantly, while the risk of recurrence is greater in ER-negative disease in the first few years, recurrence is increased in later years for ER-positive disease,” he noted (Saphner et al. J Clin Oncol. 1996; 14:2738).

In another study, Chia and colleagues conducted a retrospective review evaluating the risk of relapse in patients with low-risk node-negative early-stage breast cancer who did not receive adjuvant therapy. The results showed an unexpectedly high risk of relapse (12%) and relapse-associated death (7%) within 10 years postsurgery, even in patients with node-negative, < 1cm tumors. Increased tumor size and grade were associated with significantly increased risk of relapse (> 25%) and death (> 10%) at 10 years (Chia et al. J Clin Oncol. 2004;22:1630).

In patients who had operable breast cancer, Hortobagyi and colleagues recently reported a retrospective analysis of patients who were relapse-free at least 5 years postdiagnosis. All patients had received anthracycline-based chemotherapy, and endocrine therapy when indicated. This analysis showed a substantial risk of recurrence beyond standard adjuvant treatment. “In persons with stage II disease, the recurrence rate was 13% by year 10 and 21% by year 15. In stage III disease, these rates were 18% by year 10 and 30% by year 15. In addition, ongoing recurrence after 5 years was greater in patients with ER/PR-positive than with ER/PR-negative tumors,” Dr. Mamounas summarized (Update of Hortobagyi et al. Proc Am Soc Clin Oncol. 2004;23:23).

In addition, an Early Breast Cancer Trialists’ Collaborative Group meta-analysis analyzed 55 trials, and compared adjuvant tamoxifen versus no adjuvant therapy.
treatment in early breast cancer. “These results showed significant recurrence rates at 5, 10, and 15 years postdiagnosis in both the tamoxifen and control groups, and more than 50% of breast cancer recurrences and deaths occurred post-tamoxifen treatment,” Dr. Mamounas said (Lancet. 1998;351:1451).

In the NSABP B-14 trial, Fisher and colleagues randomized patients with ER-positive, node-negative operable breast cancer to receive adjuvant tamoxifen or placebo for 5 years. After 5 years, patients were again randomized to receive either tamoxifen or placebo through 10-year follow-up. “This study clearly shows that use of adjuvant tamoxifen is effective in reducing recurrence, but use beyond 5 years offers no additional benefit,” the speaker noted (Fisher et al. Lancet. 2004;364:838). Another multivariate analysis from the Edinburgh Breast Unit Database investigated risk factors for relapse in women who were relapse-free after 5 years of tamoxifen treatment and identified patients likely to benefit from additional therapy with an aromatase inhibitor. “These findings showed that tumor size, grade, and node status were important predictors of recurrence, with node status being the strongest predictor for late recurrence,” Dr. Mamounas said (Update of Cameron et al. Breast Cancer Research Treat. 2004; 88(suppl 1):S22).

Future Directions
In closing, Dr. Mamounas emphasized that the “risk of early breast cancer recurrence remains substantial well beyond 5 years postdiagnosis, with more than 50% of recurrences occurring after completion of adjuvant tamoxifen therapy.” Further study is needed to determine which patients may benefit from additional adjuvant endocrine therapy, such as aromatase inhibition, once tamoxifen therapy is completed.

Weighing the Options: Recent Advances in Adjuvant Endocrine Treatment

The standard use of tamoxifen for the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer has been highly effective in reducing recurrence and improving survival. “However, recent evidence suggests that consideration of other endocrine therapies, such as aromatase inhibitor agents, is also warranted to ensure optimal treatment and outcomes in this patient population,” according to Nuhad K. Ibrahim, MD, Associate Professor of Medicine, Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston.

Tamoxifen and Aromatase Inhibitors: Advantages and Disadvantages
Adjuvant tamoxifen and aromatase inhibitor endocrine therapies each have potential benefits and risks for use in postmenopausal women with hormone receptor-positive early breast cancer (Table 1). Four major studies of adjuvant therapy with aromatase inhibitors have been conducted to demonstrate both efficacy and safety outcomes.

In the ATAC trial, postmenopausal women were randomized to receive adjuvant tamoxifen or anastrozole. After 68 months of follow up, disease-free survival, prevention of contralateral breast cancer, and time to recurrence were significantly superior in patients receiving anastrozole. Time to distant metastasis and overall survival rates were comparable in both groups. “In addition, the benefit of anastrozole appeared to be greater in estrogen receptor [ER]-positive/progesterone [PgR]-negative versus ER-positive/PgR-positive tumors,” Dr. Ibrahim pointed out. In terms of side effects, both agents were well tolerated. Anastrozole was associated with fewer hot flashes, weight gain, vaginal bleeding, vaginal discharge, endometrial carcinoma, and vascular events. However, anastrozole was associated with increased long-term bone loss, while tamoxifen was associated with fewer musculoskeletal events and bone fractures (Update of Howell. Breast Cancer Res Treat. 2004; 88(suppl 1):S7).

In the four-arm randomized BIG 1-98 study, postmenopausal women with hormone receptor-positive breast cancer received adjuvant tamoxifen for 5 years; letrozole for 5 years; tamoxifen for 2 years followed by letrozole for 3 years; or letrozole for 2 years followed by tamoxifen for 3 years. Preliminary results show that letrozole significantly increased disease-free survival and was associated with increased bone fractures and decreased venous thromboembolic effects compared with tamoxifen. “While the total number of deaths was not statistically different between the two arms, cardiovascular deaths were numerically fewer in the tamoxifen arm [13 vs 26 deaths], a finding that warrants further investigation,” Dr. Ibrahim said (Thurlimann. Presentation, Ninth International Conference on Primary Therapy of Early Breast Cancer. January 2005, St Gallen, Switzerland).

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<thead>
<tr>
<th>Therapy Type</th>
<th>Potential Benefit</th>
<th>Potential Risk</th>
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<tr>
<td>Adjuvant Tamoxifen (5 years)</td>
<td>• Improved DFS and OS</td>
<td>• Agonist effect</td>
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<td></td>
<td>• Route and mode of administration</td>
<td>• Increased endometrial cancer</td>
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<td></td>
<td>• Good general tolerability</td>
<td>• Increased risk thromboembolism</td>
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<td></td>
<td>• Agonist effect on bone</td>
<td></td>
</tr>
<tr>
<td>Adjuvant Aromatase Inhibitor (long term)</td>
<td>• Potentially superior efficacy</td>
<td>• Increased bone fracture rate</td>
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<tr>
<td></td>
<td>• Less severe long-term side effects in endometrial cancer, thromboembolism</td>
<td>• Treatment-induced bone loss</td>
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<td>• Fewer hysterectomies</td>
<td>• Arthromyalgia</td>
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<td>• Cognitive disturbance</td>
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<td>• Vasomotor side effects</td>
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Nuhad K. Ibrahim, MD
The Intergroup Exemestane Study researchers investigated the sequential use of tamoxifen and exemestane. Postmenopausal patients with hormone receptor-positive breast cancer who received adjuvant tamoxifen for 2 to 3 years were then randomized to receive either tamoxifen for an additional 2 to 3 years or exemestane for 2 to 3 years. In the group that switched to exemestane, disease-free survival was increased by 27%, for an absolute benefit of 4.7%. There was also a significant reduction in contralateral breast cancer incidence, but no significant improvement in overall survival, in those receiving exemestane. “The side effect profile indicated musculoskeletal events, myocardial infarction, and diarrhea to significantly favor tamoxifen. Gynecologic symptoms and thromboembolic events favored exemestane. However, osteoporosis and rate of fractures were not statistically different between the two arms of the study, $P = 0.3$ and 0.06, respectively [St. Gallen 2005],” Dr. Ibrahim summarized (Update of Coomes et al. Breast Cancer Res Treat. 2004;88(suppl 1):S7).

In the last study, the MA.17 trial, patients who had received adjuvant tamoxifen for 5 years were randomized to receive either letrozole, placebo, or continued tamoxifen therapy for an additional 5 years. After a median 2.4 years, the results demonstrated a significant 43% decrease in risk of recurrence with letrozole compared with placebo. In addition, this effect was observed in both node-positive (40% decrease) and node-negative (53% decrease) disease. “Importantly, this study showed letrozole to be well tolerated. There was an increase in new-onset osteoporosis with letrozole [5.8% vs 4.5%], but no significant difference in bone fracture rates between letrozole and placebo,” Dr. Ibrahim explained. “This study is important because it is the first to show a significant increase in disease-free survival and significant reduction of the distant metastasis and a significant improvement in the overall survival in node-positive patients receiving letrozole, compared to the placebo arm as extended adjuvant endocrine therapy setting in postmenopausal women with hormone receptor-positive breast cancer,” he noted (Goss et al. N Engl J Med. 2003;349).

**Future Directions**

In closing, Dr. Ibrahim noted that consideration of crossover to extended adjuvant aromatase inhibitor therapy is warranted in postmenopausal women who are completing adjuvant tamoxifen therapy for breast cancer. He stressed the need for further research to determine optimal sequencing and time to crossover as well as long-term toxicity of aromatase inhibitor agents.

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**Continued Efficacy: The Use of an Aromatase Inhibitor in the Extended Adjuvant Setting**

It is known that women diagnosed with breast cancer are at risk for recurrence well beyond the 5 years after diagnosis or completion of adjuvant tamoxifen therapy. “In estrogen receptor-positive disease, the risk of late recurrence is even greater than in estrogen receptor-negative disease,” said Nicholas J. Robert, MD, Chair, Breast Cancer Committee, US Oncology Research Network, Fairfax-Northern Virginia Hematology/Oncology, Fairfax, Virginia. According to Dr. Robert, “Recent evidence indicates that use of endocrine therapy with an aromatase inhibitor after adjuvant tamoxifen therapy may afford increased efficacy in reducing recurrence and death in postmenopausal women with hormone receptor-positive breast cancer.”

**Breast Cancer Recurrence**

Breast cancer recurrence after adjuvant tamoxifen is approximately 2% and 4% per annum in node-negative and node-positive disease, respectively. While studies have shown no benefit to extending the use of tamoxifen beyond 5 years (Fisher et al. J Natl Cancer Inst. 2001;93:684), research of extended adjuvant aromatase inhibitor therapy has been promising.

**The MA.17 Data**

In the MA.17 trial, the North American Breast Intergroup and others randomized postmenopausal women who had completed adjuvant tamoxifen therapy for early breast cancer to receive either letrozole or placebo for 5 additional years. The results revealed reduced recurrence (by 42%), distant disease recurrence (by 40%), and occurrence of contralateral breast cancer (by 37.5%) compared with placebo. “Importantly, the extended adjuvant use of letrozole resulted in a significant reduction in recurrence and increase in disease-free survival. In addition, letrozole was associated with a 39% reduction in mortality over placebo in patients with node-positive disease,” Dr. Robert noted. In terms of adverse events, the incidence of new-onset osteoporosis was slightly greater in the letrozole than placebo arm (8% vs 5%); however, bone fractures were comparable between the two groups (5.3% vs 46%) (Goss et al. ASCO, 2004: Abstract 847). As part of an MA.17 companion trial, Perez and colleagues analyzed bone mineral density and bone biomarkers in the letrozole and placebo groups, and noted a decrease in decreased BMD in the lumbar sacral region, but not in the total hip (Perez et al. SABCS, 2004: Abstract 404). “This is a finding that requires further study to determine any long-term bone loss and fracture risk,” Dr. Robert said.

**Future Directions**

In closing, Dr. Robert emphasized the need to confirm menopausal status before treatment with endocrine therapy and to continue research in the areas of optimal patient selection and treatment duration, sequencing, and long-term safety profile in aromatase inhibitor therapy. Current recommendations for the use of aromatase inhibitor therapy in breast cancer can be obtained from the American Society of Clinical Oncology (Winer et al. J Clin Oncol. 2005;23:619).
IL-2, Vaccines, and Cell-Based Immunotherapy: What the Future Holds

At a recent industry-sponsored symposium held in conjunction with the 58th Annual Cancer Symposium of The Society of Surgical Oncology, four leaders in surgical oncology presented the latest data on immunotherapy for advanced melanoma and renal cell carcinoma. Topics included vaccination, adoptive cell transfer, and combination treatment modalities.

Immunotherapy has been shown to cure metastatic melanoma and renal cancer, with high-dose interleukin (IL)-2 treatment resulting in overall response rates of approximately 20% and complete response rates of 5% to 8%, said James Yang, MD, Surgery Branch, National Cancer Institute, Bethesda. According to Dr. Yang, “When considering future immunotherapy strategies, complete response—and ultimately cure—is the treatment goal. Thus, it is important to strive to induce the regression of advanced cancer in a way that is durable and clinically meaningful” (Rosenberg et al. Ann Surg. September 1998).

Based on in vitro and animal studies, several hypotheses have been proposed to explain how IL-2 may act upon cancer cells (Table 1). Importantly, the application of enhancements to T-cell function includes both agonistic and antagonistic factors (Table 2). Dr. Yang provided an overview, focusing on agonistic enhancements in the treatment of melanoma and renal cell cancer.

### Table 1. IL-2 Efficacy in Melanoma and Renal Cell Carcinoma: Proposed Hypotheses

- Rejection of advanced cancer with IL-2 is mediated by immune cells
- Tumor-reactive T cells are a likely effector population
- Generating such T cells and applying known enhancements to T-cell function augments tumor rejection

### Table 2. IL-2 Efficacy: Agonistic and Antagonistic Factors in Enhancement to T-Cell Function

**Agonistic Factors**
- Vaccination: Increases and activates tumor-reactive T cells in vivo
- Cytokines: Promote T-cell proliferation, activation, and migration
- Costimulation: CD28, 4-1BB, OX40
- T-cell adoptive transfer: Utilizes tumor-specific T cells activated and expanded in vitro

**Antagonistic Factors (to be neutralized)**
- Inhibitory receptors: CTLA4, PD-1
- T-regulatory cells: CD4+CD25+ T cells
- Inhibitory cytokines: TGF-alpha, IL-10, IL-13

**Vaccination**

According to Dr. Yang, there are several approaches to vaccination to achieve the regression of malignancy, including the use of native and modified tumor cells, dendritic cells, minimal determinant peptides, recombinant viruses, heat shock proteins, purified proteins, and DNA. “The major obstacle with vaccination is that we do not accomplish treatment goals using our current methods. In addition, even when effective vaccination is achieved, it is unlikely to be sufficient to affect bulk disease in any type of cancer,” Dr. Yang said (Rosenberg et al. Nature Medicine. September 2004).

In one animal study, Restifo and colleagues genetically inserted a T-cell receptor recognizing the murine gp100 tumor antigen into every T cell of a mouse. “When B16 melanoma expressing gp100 was injected into these transgenic mice and their non-transgenic littermates, tumors grew identically despite the fact that every one of the T cells in the transgenic TCR mice could recognize this tumor. This indicates...”
that CTL precursors alone are not adequate to prevent the outgrowth of newly implanted antigen-positive tumor,” Dr. Yang said. To show that these transgenic T cells could indeed work, Restifo’s group treated B16-bearing mice with either no treatment; control transgenic T cells plus vaccine plus IL-2; gp100-reactive transgenic T cells plus a control vaccine plus IL-2 or gp100-reactive transgenic T cells (fresh or cultured) plus a gp100 vaccine plus IL-2. “These results showed significant regression of large established tumors only when the appropriate cells and vaccine and IL-2 were combined.” Dr. Yang explained. According to Dr. Yang, identification of the appropriate stimulation for T-cell precursors is both the challenge and current failing of vaccine therapy (Overwijk et al. J Exp Med. August 2003).

Dr. Yang pointed out that vaccination as therapy for advanced melanoma, renal cell carcinoma, and other malignancies—especially in combination with other treatment modalities—continues to be a promising area of study. The results of numerous ongoing clinical studies are awaited.

**T-Cell Adoptive Transfer**

Another promising new technique in immunotherapy is T-cell adoptive transfer. In one recent study, Dudley and colleagues treated patients with metastatic melanoma via adoptive transfer with highly selected tumor-reactive T cells directed against over-expressed self-derived differentiation antigens after a nonmyeloablative conditioning regimen. The results showed both cancer regression and clonal repopulation with autologous lymphocytes (Dudley et al. Science. October 2002).

In addition, previous research of treatment with tumor-infiltrating lymphocytes plus IL-2 in persons with melanoma has shown a response rate of 34%. However, this response was short lived in many patients (Rosenberg et al. JNCI. 1994). “The next step is the addition of host immunosuppression to reduce competition of resident lymphocytes for nutrients and cytokines; to stimulate host restorative/homeostatic support of proliferation of transferred T cells; and to promote the depletion of host T-regulatory cells,” Dr. Yang said.

The Surgery Branch, NCI, has treated patients with melanoma by integrating preparative nonmyeloablative chemotherapy with adoptive T-cell transfer. After chemotherapy and profound immunosuppression, TIL transfer and supportive systemic IL-2 therapy were administered. “Many patients had good responses, with a rebound of peripheral blood counts, repopulation of melanoma-specific T cells, and both modest and dramatic clinical responses with regression of metastatic lesions,” Dr. Yang explained (Dudley et al. JCO. April 2005). Dudley and colleagues treated 35 patients with melanoma with chemotherapy (CYFlu) plus TIL plus IL-2, revealing a complete response rate of 11% and major response rate of 51%. “This response was likely due to the administration of cultured autologous T cells—perhaps the result of active T-cell recognition of common shared antigens such as MART-1, gp100, or autologous tumor,” Dr. Yang noted.

**CTLA4 Blockade in Melanoma Immunotherapy**

Immunotherapy is an effective treatment option for select patients with metastatic melanoma. However, certain antagonistic factors—including the inhibitory receptor CTLA4—can act to inhibit the efficacy of immunotherapy.” Thus, blocking the inhibitory effect of CTLA4 may allow for enhanced efficacy and anti-tumor regression in persons with melanoma undergoing immunotherapy,” said James S. Economou, MD, University of California, Los Angeles.

**Goal of CTLA4 Blockade**

In the presence of immunotherapy, activated T cells upregulate CTLA4, which may in turn deliver a negative regulatory signal. “The hope is that administration of a blocking antibody will allow for the interruption of this negative regulatory signal, thereby achieving more robust clonal expansion and T-cell activation,” Dr. Economou explained.

**Preliminary Data**

In one study, Economou and colleagues treated patients with a dendritic cell vaccine (with single melanoma antigen) and a CTLA4-blocking antibody. ELISPOT assays showed a sustained expansion of MART1 T cells as well as T-cell responses to two other melanoma-expressed antigens, gp100 and tyrosinase. “This phenomenon, called determinant spreading, is an important feature of the anti-tumor response,” Dr. Economou said. CTLA4 blockade also prompted T-cell response to antigens from past exposures, such as the influenza virus. “It may be the initial expansion of MART-reactive T cells that attacks the melanoma cells. The cancer cell debris is taken up by dendritic cells, is processed, and is then expanded in a second wave of vectors recognizing gp100 and tyrosinase,” he summarized.

In a phase I dose-escalation trial, a single dose of CTLA4 antibody was administered to patients with melanoma, many of whom were pretreated. The maximum dose was 15mg/kg, and adverse effects included rash, diarrhea, autoimmune diabetes mellitus, colitis, fatigue, autoimmune disorders, hyperpituitarism, and hypothyroidism. Responses included two disease stabilizations at low doses, one complete response at 3mg/kg, one partial response at 10mg, and two complete responses at 15mg.

In a currently ongoing trial at UCLA, three patients with melanoma have received a MART1 dendritic cell vaccine as well as concurrent and subsequent CTLA4 blockade therapy in a dose-escalating protocol. Preliminary clinical responses appear promising, and further results are awaited. “Our hypothesis is that CTLA4-blocking antibody provides a stronger activating signal to T cells by curbing the inhibitory signal to CTLA4,” Dr. Economou noted.

**Future Directions**

In closing, Dr. Economou emphasized the need for further study of CTLA4 blockade in combination with dendritic cell vaccination and other immunotherapy approaches. “Dramatic responses in select patients with metastatic melanoma point to the need for continued study of both agonistic enhancements and antagonistic factor inhibition in the treatment of this challenging disease,” he concluded.
IL-2 Therapy: Dose Selection and Opportunities for Patient Selection

Immunotherapy with interleukin-2 (IL-2) continues to play an important role in the treatment of select patients with advanced melanoma or renal cell carcinoma. Essential to the optimal utilization of this treatment modality is the identification of selection factors for dose, predictors of response, and patients who are most likely to benefit, said Michael Atkins, MD, Director, Cutaneous Oncology and Biologic Therapy Programs, Beth Israel Deaconess Medical Center, and Renal Cancer Program and SPORE Dana Farber/Harvard Cancer Center, Boston, Massachusetts.

Considerations in Dosing
High-dose IL-2 therapy was approved by the US Food and Drug Administration (FDA) for use in persons with renal cell carcinoma in 1992 and melanoma in 1998. In the treatment of renal cell carcinoma, the response rate is approximately 15%, with few relapses occurring after 30 months. In melanoma, the response rate is approximately 16%, with 11% of patients surviving at least 5 years (Atkins et al. JCO, 1999). “While high-dose IL-2 therapy produces durable responses in a portion of patients, it can also have substantial toxicity, making lower-dose IL-2 combination therapy an attractive subject of study,” Dr. Atkins said.

Melanoma
In one phase III trial, Eton and colleagues compared sequential biochemotherapy to chemotherapy alone. The results showed a doubling of response rates and time to progression with the sequential regimen; however, toxicity was too great for widespread use (Eton et al. J Clin Oncol. 2002; 20:2045).

Legha and colleagues found similar activity, but no increased organ toxicity, using concurrent chemotherapy, IL-2, and interferon (Legha et al. Cancer J Sci Am. 1997;3(suppl 1); S9). However, a recent intergroup study observed increased toxicity and no improvement in response duration or overall survival with a biochemotherapy regimen versus chemotherapy alone. (Atkins et al. Proc Am Soc Clin Oncol. 2003; 22:708a).

Renal Cell Carcinoma
In the treatment of renal cell cancer, Yang and colleagues compared high-dose IL-2 and low-dose IL-2, while McDermott and colleagues studied high-dose IL-2 versus low-dose IL-2 and interferon. The results of these two phase III trials were similar, with improved response rates and duration of response in the high-dose arms. “In addition, subsets of patients did show survival advantages relative to low-dose IL-2 and interferon. In those with liver or bone metastases or primary tumor in place the median survival was significantly greater in the high-dose IL-2 arm,” Dr. Atkins said. (McDermott et al. J Clin Oncol. 2003; 23:133).

According to Dr. Atkins, this suggests that high doses of IL-2 may be necessary to overcome the tumor-induced immune suppression in these disease sites. “IL-2 remains the only immunotherapy approved by the FDA for the treatment of metastatic renal cell cancer and melanoma. While high-dose IL-2 continues to be the preferred regimen for appropriately selected patients with advanced melanoma and renal cancer, future research is needed in the areas of maintenance immunotherapy, vaccine combinations, biochemotherapy, adoptive immunotherapy, and reversal of immune suppression,” Dr. Atkins summarized.

Issues in Patient Selection
“An important component in ensuring the optimal use of IL-2 in persons with cancer is the identification of those who will and will not benefit from this therapy,” Dr. Atkins said. Multiple opportunities exist for patient selection for IL-2 therapy in both renal cell cancer and melanoma (Table 1).

Renal Cell Cancer
One area of molecular study aiding in selection of patients with renal cell cancer is carbonic anhydrase IX (CAIX) expression. High CAIX-expressing tumors are not only associated with response to IL-2, but also longer survival. CAIX staining has been shown to enhance the predictive information from pathology specimens, and has yielded response rates of 30% to 40% in patients with high-expressing and good or intermediate prognosis pathology tumors versus < 5% in patients with low-expressing, intermediate or poor prognosis pathology specimens,” Dr. Atkins said. A two-component model, consisting of pathology review and CAIX staining, requires prospective validation. Additional information could be obtained from other immunohistochemical stains and pAKT staining where preliminary data suggest that high glut-1 is associated with increased survival, while high pAKT staining is linked with failure to respond to IL-2 therapy (Atkins et al. Clinical Cancer Res. 2005, in press).

Another emerging technique in patient selection is gene expression profiling, which has tremendous potential to assist in predicting response and non-response to IL-2 in persons with renal cell cancer. This technique may provide information about potential novel biomarkers; treatment mechanism of action; coordinate gene expression and tumor biology; and correlation with clinical, pathologic, IHC, SNP, SSO Symposia Highlights

Table 1. Opportunities for Patient Selection for IL-2 Treatment

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<th>Renal Cell Cancer</th>
<th>Melanoma</th>
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<td>General (TCR zeta chain level, arginase, IDO, Tregs)</td>
<td>Specific (T-cell reactivity)</td>
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Michael Atkins, MD
and proteomic data. Preliminary data suggest that MnSOD and IL-1 receptor antagonist expression may be increased in tumors of non-responders, while tumors from responding patients appear to have high TIMP3 expression (Febbo et al. J Immunother. 2004;27:6,S12). These observations require validation, but do raise the possibility that other markers predictive of response will be identified.

**Melanoma**

In patients with melanoma, numerous factors have been cited as potentially useful in predicting response to IL-2 therapy (Table 1). Wang and colleagues performed fine-needle aspiration of metastases of persons receiving IL-2. “These findings indicated 30 genes that were predictive of response, with half related to T-cell regulation, suggesting that immune responsiveness might be predetermined by a tumor microenvironment conducive to immune recognition,” Dr. Atkins explained (Wang et al. Cancer Res. 2002; 62:3381).

In closing, Dr. Atkins stressed the tremendous potential to identify predictors of response and therefore to limit IL-2 treatment to patients with renal cell cancer or melanoma who are most likely to benefit from this therapy. “Additional efforts to identify further selection factors, including tumor tissue and immune cell characteristics, are needed to optimize treatment of this patient population,” he concluded.

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**Immunotherapy with Peptide Vaccination in Melanoma**

The continued study of immunotherapy strategies, including peptide-based vaccination, is essential to advancing the treatment options for patients with melanoma,” said Craig L. Slingluff, Jr, MD, Professor of Surgery, Division Head, Division of Surgical Oncology, University of Virginia Health Systems Cancer Center, Charlottesville. According to Dr. Slingluff, recognition of the complex host-tumor interplay is key to understanding the mechanisms of immune escape, tumor-induced tolerance, and clinical response to immunotherapy. Dr. Slingluff provided an overview of the current and future directions for peptide-based vaccination in melanoma.

**Peptide-Based Vaccination: Advantages and Challenges**

Peptide-based vaccinations offer several potential advantages in the treatment of melanoma, including use in patients without measurable disease, generation of early immune response, use in prevention of disease, portability, and low cost. The challenges of this type of vaccination include the heterogeneity of HLA types in patient populations. “Thus far, HLA-A1, A2, and A3 have been targeted, accounting for approximately 80% of patients with melanoma in the United States,” Dr. Slingluff noted. Another challenge is the heterogeneity of antigen expression. “Targets include the downregulation of melanocytic differentiation protein (MDP) expression in metastases and expression of cancer-testis antigens (CTA) that are present in subsets of melanomas and are increased in metastatic lesions,” Dr. Slingluff said. Other challenges of peptide vaccination include optimal patient selection; patient monitoring; and incomplete understanding of dendritic cell function inhibition, targeting T cells to the tumor, and T-cell stimulation and regulation. “Importantly, utilizing multiple peptide-based vaccines in combination with other therapies may be the most effective approach to overcoming these barriers,” the speaker said.

**The Multipepptide Approach**

Due to the heterogeneity of HLA types and antigen expression in melanoma, Slingluff and colleagues have utilized a 12-peptide vaccine, including four HLA-A1, four A2, and four A3 peptides. Thus far, vaccination with this multipepptide vaccine has produced immune responses to 10 of the 12 peptides, with more than 50% and up to 89% of patients developing an immune response to certain peptides. There has been no observation of significant inhibition of immune response based on competition for binding to the same MHC molecule (Slingluff et al. J Clin Oncol. 2004; 22 (14S): 7503).

“It is hoped that vaccination with 12 peptides—and in the future with larger peptide cocktails—will increase the total CTL reactivity against tumor antigens,” Dr. Slingluff explained. According to Dr. Slingluff, multipepptide vaccination allows the induction of peptide reactive responses in the blood that are represented as activated T cells. “While most of the work to date has not targeted melanoma-reactive helper T cells, clearly this is an important direction of future research,” he noted.

**Multiple Helper Epitopes**

Multiple helper epitopes are known to combine to multiple different class 2 MHC molecules. Slingluff and colleagues are conducting one phase I trial in which patients with advanced or high-risk melanoma expressing HLA-DR1, 4, 11, 13, or 15 are vaccinated with a mixture of six different melanoma helper peptides. The preliminary data are encouraging, showing immune responses to all six peptides in the cocktail vaccine, and immune responses in four of the five patients. “In most patients who responded to the peptides, a balanced Th1-Th2 response was observed, with slight Th1 dominance. Occasionally, a highly dominant Th1 response was also observed without any Th2 response to certain peptides,” Dr. Slingluff explained.

**Future Directions**

In closing, Dr. Slingluff noted that the peptide vaccines can induce T-cell responses to multiple antigens expressed on tumor cells, help induce an immune response, and that T cells generated from vaccine patients can lyse tumor cells. Further study is needed to determine whether vaccine-induced T cells can infiltrate the tumor reliably. “In addition, the advancement of effective treatment options for patients with melanoma requires further research in several areas, including 1) vaccination combined with other immunotherapy/chemotherapy approaches and 2) technology to assess the complexity of the pathophysiology of the host-tumor relationship,” he concluded.
Systemic Chemotherapy Options for Colorectal Cancer

The past 5 years have brought tremendous progress in the chemotherapy and biologic agents available for the treatment of colorectal cancer. “It is hoped that outcomes for patients with metastatic colorectal cancer will continue to improve with advances in surgical techniques, additional options in combination chemotherapy and biologic agents, improvement in convenience with oral agents, and reduction in toxicity,” said Daniel G. Haller, MD, Professor of Medicine, Abramson Cancer Center, University of Pennsylvania, Philadelphia.

**Systemic Chemotherapy Options**

Currently, multiple standard treatment options are available for the treatment of colorectal cancer (Table 1). While 5-fluorouracil (5-FU)/leucovorin (LV) remains the core of medical treatment for this disease, several newer agents have led to improved survival in this patient population. The US Food and Drug Administration (FDA) approved irinotecan plus 5-FU/LV as first-line therapy in 2000, and oral capecitabine (5-FU prodrug) in 2001. Oxaliplatin plus 5-FU/LV was approved as second-line therapy in 2002 and as first-line therapy in 2004. Oxaliplatin was also approved as a monotherapy in patients with stage III disease who could not tolerate or did not respond to 5-FU/irinotecan.

These agents have been demonstrated to be synergistic. In the United States, 70% of patients receive first-line 5-FU/oxaliplatin; however, the optimal sequencing of agents for use in metastatic colorectal cancer is not yet known, Dr. Haller noted. In many cases, comorbidity may determine treatment sequence. For example, a patient...
Advanced Colorectal Cancer: Downstaging to Allow Resection

In the United States, nearly 150,000 people are diagnosed with colorectal cancer each year, and approximately 50% of these present with liver metastasis. “In patients with liver metastasis, resection is the preferred mode of treatment, with 5- and 10-year survival rates [32% and 23%, respectively] being superior to those of systemic chemotherapy or no treatment,” said Rene Adam, MD, Hepato-Biliary Center, Paul Brousse Hospital, Villejuif-Paris, France. According to Dr. Adam, “Unfortunately, a majority of patients present with initially unresectable metastasis, making the downstaging of disease important to allowing resection and achieving optimal outcomes for patients with advanced colorectal cancer.” Importantly, secondary and repeat partial hepatectomies are associated with the same long-term survival benefit.

Downstaging of Disease

The survival benefit of neoadjuvant chemotherapy for initially unresectable liver metastasis has been clearly demonstrated. In one study, the majority of > 1100 patients presented with initially unresectable liver metastasis and were treated with chemotherapy, mainly the FOLFOX regimen. Following chemotherapy, 13% of those with initially unresectable disease were able to undergo surgical resection. The 5-year survival rate in patients undergoing secondary resection was 33%, and in those undergoing primary resection, 48%. The 10-year survival rates were 23% and 30%, respectively. Compared with a control population, no major differences in morbidity or mortality were observed. “These findings demonstrate the importance of avoiding limited primary resection of unresectable metastasis, as chemotherapy may be successfully used to downstage disease and achieve full resection,” Dr. Adam said (Adam et al. Ann Surg. 2004; 240, 4:644).

While neoadjuvant chemotherapy is the most important tool in downstaging initially unresectable disease, response is sometimes insufficient to achieve resection. In these cases, portal embolization is a technique that may offer hope. Other means consist to combine resection with cryotherapy or radiofrequency ablation to allow partial hepatectomy or to perform a two-stage hepatectomy. “For patients with multiple unilobar disease with a projected remnant liver of less than 30%, portal embolization before resection may be indicated. For those with multiple bilobar disease and a future remnant liver with up...
Liver Metastasis: Methods to Improve Resectability

The survival rates after resection of colorectal cancer-associated hepatic metastasis continue to improve, likely due to a combination of advances in imaging techniques, patient selection, and surgical technique,” said Jean-Nicolas Vauthey, MD, Chief of Liver Service, and professor of surgery at The University of Texas M.D. Anderson Cancer Center in Houston, Texas. Dr. Vauthey provided an overview of prognostic factors believed to influence patient outcomes after resection of hepatic metastasis of colorectal cancer.

Extent of Resection

“In evaluating the extent of liver resection, the size of the future liver remnant is a primary determining factor,” Dr. Vauthey noted. Based on computer tomography (CT) three-dimensional reconstruction, preoperatively measured future liver volume correlates with postoperative liver function tests, bilirubin, prothrombin time, alkaline phosphatase, and patient length of stay. “Indeed, one 2002 study indicated an increase in complication rates by more than 50% in patients with a future liver volume equal or less than 20%,” Dr. Vauthey said. These findings point to the importance of ensuring projected liver remnant volume equal or less than 20%,” Dr. Vauthey explained. To address concern over potential to increase tumor growth, Vauthey and colleagues analyzed a series of patients undergoing portal vein embolization. The findings showed an increase in future liver remnant volume. However, there was no significant increase in tumor growth or progression to unresectable status during the 3-week waiting period (Vauthey et al. Surgery. 2000; 127:512).

Role of Chemotherapy

Dr. Vauthey cautioned that positive margins may be a concern in some cases of primary resection. However, in patients undergoing preoperative chemotherapy, Vauthey and colleagues observed a lower percent of positive margins in spite of multiple tumors. “This may be the result of downstaging and/or selection of patients,” he noted.

In approximately 10% of patients with unresectable liver metastasis, effective downstaging of disease with neoadjuvant chemotherapy may allow for successful resection (Parikh et al. J Gastrointest Surg. 2003; 7:1082).

Role of Radiofrequency Ablation

In patients with multiple bilobar involvement without bi-segmental sparing, radiofrequency ablation may be an option when resection is not feasible. “Radiofrequency ablation is used selectively, and a combination of this technique with major resection is utilized with caution due to potential damage to the future liver remnant,” Dr. Vauthey explained. In one study, a comparison of resection versus radiofrequency ablation plus resection versus radiofrequency ablation alone showed an increase in local recurrence rate and intrahepatic recurrence rate in the radiofrequency groups. “Resection remains the first choice, and radiofrequency ablation the second choice, in this patient population,” the speaker summarized. In patients with solitary hepatic metastasis, further study is needed to identify the recurrence and disease-free survival rates of radiofrequency ablation versus neoadjuvant chemotherapy options (Abdalla et al. Ann Surg. 2004; 239:818).

Indicators of Prognosis

“Unfortunately, existing clinical factors are not sufficient to predict prognosis in persons with hepatic liver metastases,” the speaker noted. Vauthey and colleagues are currently investigating the use of telomerase to predict survival after hepatic metastasis resection. The hTRT component of telomerase indicates cell immortalization and resistance to apoptosis. In their multicenter study, the researchers evaluated hTRT in 201 patients, and found a
Treatment Options for Hepatic Colorectal Metastases

Partial hepatectomy is the gold standard for treatment of hepatic colorectal cancer metastases. “However, multiple neoadjuvant and adjuvant treatment options are also available, and several key questions remain regarding the management of colorectal cancer liver metastases,” said Graeme Poston, MD, University Hospital Aintree, Royal Liverpool University Hospital, Liverpool, United Kingdom (Table 1). Because no consensus has been achieved for the optimal management of colorectal cancer hepatic metastases, Prof. Poston and colleagues developed a computer-based management model to assist in this decision-making process.

**Development of Decision Model**
Because no consensus exists on the appropriate management of colorectal cancer liver metastases and the results of ongoing or planned clinical trials are years away, Poston and colleagues developed a benefit-risk decision model to: 1) identify and individualize resectability for patient populations, and 2) make recommendations for the optimal treatment of colorectal cancer liver metastases on an individual basis.

The first step of developing this model was the assembly of a multidisciplinary panel of experts (eg, surgeons, oncologists, radiologists) to review current research evidence, establish appropriate treatment options, and identify all possible patient characteristics for the database. Based on the panel’s input, the RAND/UCLA Appropriateness Method was then used to assess whether a medical or surgical intervention is: appropriate (expected benefits exceed expected risks), inappropriate (no health benefit), or uncertain (benefits and risks are nearly equal).

**Contraindications and Treatment Indicators**
The panel identified contraindications for resection, including unresectable extrahepatic disease, extensive liver involvement (>6 segments, >70% liver parenchyma, or all three hepatic veins), major liver insufficiency, or patient who is unfit for or declines surgery. Patient prognostic characteristics not considered contraindications to resection included age, sex, CEA, site of primary tumor, T stage of primary after R0 resection, adjuvant chemotherapy after primary resection, and synchronous versus metachronous detection. Patient indicators considered to impact the decision to resect included number of metastases, size of largest metastasis, lobar involvement, radiologic portal lymph node involvement, radiologically defined resection margins, potentially curable extrhepatic disease, and outcome of prior chemotherapy.

According to Prof. Poston, the analysis of appropriateness for medical or surgical intervention included both primary and secondary determinants for immediate resection, resection after preoperative chemotherapy, local destruction (few indications), and postoperative chemotherapy.

**Utilization of the Final Model**
“With the patient, clinical, and treatment factors integrated into the final decision model, the researchers were then able to enter an individual patient profile, and receive a statement on choice of strategy for management of liver metastases.”

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**Table 1.**

**Key Questions and Adjuvant Options in the Management of Colorectal Cancer Liver Metastases**

<table>
<thead>
<tr>
<th>Key Questions</th>
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<tbody>
<tr>
<td>• How to define resectability?</td>
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<td>• What is the role of tumor ablation?</td>
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<td>• How do we predict resectability after chemotherapy?</td>
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<td>• Which chemotherapy regimen is optimal?</td>
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<td>• What is the optimal timing of chemotherapy? Neoadjuvant, adjuvant, or both?</td>
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<table>
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<th>Adjuvant Options for Resectable Metastases</th>
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<td>• Systemic chemotherapy</td>
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<td>• Portal vein infusion</td>
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<td>• Neoadjuvant chemotherapy (downstaging to resectable)</td>
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