Tumor-Associated Macrophages as Targets for Cancer Therapy

Larry M. Wahl, Hynda K. Kleinman

Tumor-associated macrophages (TAMs) originate in the circulation and are recruited to the tumor site by specific tumor-derived attractants such as monocyte chemotactic protein-1 (1,2). By use of several mechanisms, TAMs bind to the tumor cells via glycoproteins, sugars, and phospholipids and become localized at the tumor–host tissue interface (2,3). Unlike macrophages that are involved in inflammation, TAMs proliferate at the tumor site. Although macrophages have the potential to mediate tumor cytotoxicity and to stimulate antitumor lymphocytes, the tumor cells can not only block the host’s defense program but also can benefit from the activities of the TAMs. In some cases, tumor-derived molecules actually redirect TAM activities to promote tumor survival and growth. Many tumor-derived factors—including interleukin (IL)-4, -6, and -10; transforming growth factor-β1 (TGF-β1); prostaglandin E2; and macrophage colony-stimulating factor—reduce the cytotoxic activity of the TAMs (4,5). TGF-β1 has also been shown to increase urokinase expression in TAMs (6). The strategic location of the TAMs also allows them to have a number of important additional effects on tumor cells. TAMs produce growth factors, including IL-1 and platelet-derived growth factor, which may directly promote tumor growth (1). Proteases secreted by TAMs degrade the surrounding tissue and could facilitate tumor cell expansion and invasion. Last, TAMs secrete factors that promote angiogenesis, including vascular endothelial growth factor, a protein that further supports the growth and spread of tumors. Thus, TAMs can either directly or indirectly contribute to tumor survival, growth, and metastasis and these cells could be a potential target for antitumor therapy. Possible strategies that involve TAMs in include reducing the number of host macrophages and/or increasing the cells’ tumoricidal activity.

In the report by Joseph and Isaacs (7), factors that reduce the number of TAMs were tested for their effects on tumor growth. These pharmacologic agents included Linomide®, thalidomide, pentoxifylline, and genistein. Linomide caused the greatest reduction of tumor volume in the Dunning R-3327 MAT-Lu rat prostate cancer model. The findings from this study, although preliminary, suggest that Linomide may suppress tumor progression by elevating the levels of plasminogen activator inhibitor type 2 (PAI-2). No association with the levels of tumor necrosis factor-α, an angiogenesis-promoting cytokine, or granulocyte–macrophage colony-stimulating factor, a cytokine that stimulates the production of PAI-2 by macrophages, was observed. As the authors indicate, Linomide may exert its tumor-suppressing activity through several additional mechanisms. One avenue for future research will be to determine the effect of Linomide on the production by TAMs of other cytokines, such as IL-12 and IL-18. The production of IL-12 by activated macrophages serves to enhance immune function by shifting CD4+ T cells toward the Th1 subset, which secretes IL-2 and interferon γ (IFN-γ). IL-12 inhibition of angiogenesis and tumor progression has, in large part, been attributed to its induction of IFN-γ, which in turn stimulates the production of interferon-inducible protein 10 (IP-10) and monokine induced by IFN-γ (MIG) (8–11). IP-10 and MIG are members of the CXC branch of the chemokine superfamily (12), and have been shown to have angiostatic activity (13). IL-18 (14), also identified as interferon γ-inducing factor (15), is—like IL-12—produced by activated macrophages and stimulates the release of IFN-γ (16). Similar to IL-12, IL-18 inhibits angiogenesis through its stimulation of IFN-γ, thus resulting in a systemic antitumor effect (17). Moreover, IL-12 and IL-18 act synergistically to induce murine tumor regression through the inhibition of angiogenesis (17). It also appears that IL-12, IFN-γ, and possibly IL-18 may inhibit tumor growth by inducing tumor cells to generate antiangiogenic activity through, as yet, unknown factors (18). Thus, it is important to determine the effect of Linomide on the production of these cytokines by TAMs. If Linomide inhibits IL-12 and IL-18 due to its immunosuppressive properties, protocols in which these cytokines and Linomide are combined would be worth pursuing.

The levels of activities of two families of proteases, the matrix metalloproteinases and the urokinases, associate positively with tumor malignancy and are also important in angiogenesis (19–22). Likewise, naturally occurring tissue inhibitors of metalloproteinases, TIMPs, have been found in various experimental systems to reduce tumor growth, metastasis, and angiogenesis (20). For example, Marimastat, a broad spectrum metalloproteinase inhibitor, is one of several inhibitors currently in clinical trials as an anticancer agent. While natural and synthetic metalloproteinase inhibitors reduce tumor growth and angiogenesis, the naturally occurring inhibitor of plasminogen activation, plasminogen activation inhibitor type 1 (PAI-1) appears to increase tumor growth by mechanisms beyond its protease-inhibition activity (23). Mice deficient in PAI-1 do not exhibit local tumor cell invasion or tumor vascularization, but when PAI-1 is given systemically, these activities are restored. In con-
trast, the antitumor effects of the other naturally occurring plasminogen activator inhibitor, PAI-2, have been documented in a variety of cancers (24–26). There is a positive association between PAI-2 levels, reduced metastases, and increased survival. The finding by Joseph and Isaacs of increased PAI-2 after Linomide treatment may explain the antitumor effects of this drug. While the data do not show a dose response, the increased PAI-2 levels appear to be the only factor that is associated with the reduction in tumor burden. These data possibly point to a new mechanism of Linomide action and further define PAI-2 as an important modulator of tumor growth and angiogenesis. The direct effects of PAI-2 and Linomide on these processes require further documentation at this time. These future studies should also be accompanied by the examination of the effect of Linomide on macrophage production of matrix metalloproteinases as well as TIMP-2, an important protease inhibitor and suppressor of tumor growth and angiogenesis.

REFERENCES

Do Human Papillomavirus Infections Cause Oral Cancer?

Keerti V. Shah

The etiologic link between infections of the genital tract with human papillomavirus (HPV) and invasive cervical cancer was established when the mutually corroborative evidence from epidemiologic, virologic, and molecular pathogenesis studies appeared to account for the characteristics of cervical cancer incidence and distribution all over the world (1). The risk factors for cervical cancer are the same as those for HPV infections. HPV types 16 and 18 that predominate in cervical cancer tissues have been shown to be the most oncogenic types in laboratory studies. The E6 and E7 genes of HPVs that are invariably expressed in HPV-associated cervical cancers have been found to code for proteins that inactivate, respectively, tumor suppressor proteins p53 and Rb and lead to genetic instability and cellular changes that underlie carcinogenesis. The integration of the HPV genome in cellular DNA, a frequent occurrence in HPV-associated invasive cervical cancer, disrupts the E1/E2 open-reading frames of the HPV genome and results in increased expression of the E6 and E7 oncogenes. As a result of the concurrence of the evidence from many different lines of investigations, the etiologic role of HPVs in cervical cancer is widely accepted.

HPV infections also seem to be related to cancers at other anogenital tract sites, e.g., the vulva, the vagina, the anal canal, and the penis, although at these sites they may account for a fraction of the cancers. However, the contribution of HPV infections to cancers at nongenital sites remains unclear. With the availability of the highly sensitive but error-prone polymerase chain reaction technology, HPV genomic sequences have been reported in cancerous tissues of many nongenital sites, which include the colon, the prostate, the breast, the ovary, the esophagus, the eye, the oral cavity, the larynx, and the lung. The difficulties in interpretation of the results of these studies are illustrated in the investigation of oral cancers. In 1995, Steenbergen et al. (2), in a case report of an oral cancer located on the floor of the mouth of a 58-year-old male patient, provided incontrovertible evidence that HPV type 16 DNA was integrated into the genome of the tumor cells of this patient and was transcriptionally active; the tumor as well as a cell line derived from it showed E6 and E7 expression, an identical pattern of HPV type 16 integration, and identical allelic losses. However, in contrast to the above case report that was strongly suggestive of a causal link between HPV type 16 infection and oral cancer, the results of a large number of other studies on the role of HPVs in oral cancer are conflicting [reviewed in (3–5)]. The HPV prevalence rates in oral cancers varied from 31% to 74% in different studies, and in five studies of carcinoma of the tongue, HPV prevalence ranged from 0% to 82% [reviewed in (4)]. Most of the studies were based on convenience samples of small numbers of oral cancers, and they lacked a detailed virologic examination of HPV-associated oral cancers [similar to that by Steenbergen et al. (2)], information on HPV prevalence in samples from uninfected controls, and analysis of the HPV data in the context of sexual history risk factors and of history of alcohol and tobacco use, known risk factors for oral cancer.

The study by Schwartz et al. (6), published in this issue of the Journal, overcomes many of the shortcomings of the previous studies. These authors examined the HPV–oral cancer question in a formal, population-based, multifaceted, case–control study of incident cases of oral cancers in which data on alcohol and tobacco use and on sexual history risk factors were obtained by structured in-person interviews, virologic examinations for HPVs were performed on oral scrapes from case subjects and from control subjects as well as on the archived tumors of the case subjects, and serum specimens from case subjects and control subjects were examined for antibodies to HPV type 16 capsid protein. They studied 284 case subjects with oral squamous cell carcinoma, newly diagnosed during the period 1990 through 1995, and 477 control subjects frequency matched with case subjects on age and sex; all subjects resided in one of three counties in western Washington State. Ninety-two percent of the case subjects had invasive carcinoma, and the remainder had in situ carcinoma. Serologic data and HPV data from archived tumor DNAs provided evidence suggesting an association between HPVs and oral cancers. The proportion of sera positive for HPV type 16 capsid antibody was 35% in control subjects, 51.4% in case subjects, and 75.7% in the 37 subjects whose tumors were positive for HPV type 16 DNA. The HPV DNA prevalence was virtually identical (9.2% and 9.3%) in oral scrapes from case subjects and control subjects but was 26% in DNAs extracted from archived case tumors. The authors point out that the low prevalence in oral scrapes from case subjects may be because these specimens were collected after the patients were treated. About two thirds of the HPV-positive tumor DNAs contained HPV type 16. The highest HPV DNA prevalence was reported for tumors of the oropharynx (n = 11) and tumors of the tonsils (n = 40). Alcohol consumption and tobacco use were strong risk factors for oral cancers, and they appeared to increase the risk of oral cancers associated with HPV type 16 capsid seropositivity. The effect of sexual history risk factors on oral cancers was equivocal. In men, but not in women, the risk of oral squamous cell carcinoma increased with increasing number of sexual partners and with a history of genital warts. History of oral sex with opposite sex partners was not associated with oral cancers, and the high prevalence of HPV type 16 DNA in tonsillar cancers reported in this study confirmed several previous reports from Europe of this association (7–9).

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A model for head and neck squamous cell carcinomas (HNSCCs—carcinomas of the oral cavity, pharynx, and larynx), based on cellular genetic changes associated with the histopathologic progression of HNSCC (10), stresses the importance of p53 mutations, which are common in HNSCC and which may be induced, in part, by exposure to alcohol and tobacco (11). Schwartz et al. (6) did not examine their oral cancers for p53 mutations. A number of recent studies in which HNSCCs were examined for HPVs as well as for p53 and/or Rb mutations and for tumor pathology extend the observations of Schwartz et al. (6) and, in addition, define a subset of HNSCC that may be etiologically linked to HPV infection (12–15). The characteristics of this subset are location predominantly in the oropharynx (base of tongue, soft palate, tonsils, and tonsillar fossa), lack of association with p53 and Rb mutations and with history of tobacco and alcohol exposure, and frequently a basaloid pathology. In view of the ability of the HPV E6 protein to inactivate p53, HPV infection may be functionally equivalent to p53 mutation. Why the HPV-associated cancers predominate in the oropharynx and how genital HPVs are transmitted to the oropharynx remain unknown. If future virologic and epidemiologic studies confirm an infectious etiology for a subset of HNSCC, patients with these tumors may benefit from HPV-based immunotherapy now being explored for the treatment of invasive cervical cancer.

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A decrease in breast cancer mortality in the United States was reported for the first time in 1994 (1). This decrease has been attributed, in part, to better adjuvant therapies that have become standard after carefully conducted, randomized, controlled trials have established a clear benefit. In reality, however, physicians and patients must also make treatment decisions in situations where optimal trial data are lacking. Appropriately, leaders in the field have met at regular intervals to provide a consensus as to how new information can be incorporated into practice. The results of the 6th International Consensus Panel on the Treatment of Primary Breast Cancer are presented in this issue of the Journal (2). There are several noteworthy differences between the recommendations from this conference as compared with those from the 1995 consensus panel that reflect both our expanding knowledge base and our changing societal attitudes toward cancer and cancer treatment. Some of these changes stem from the growing confidence that adjuvant chemotherapy can improve survival in most cases of breast cancer, even though these differences may be small in absolute terms.

**Threshold for Systemic Therapy**

To begin with, the 1998 consensus report redefined the threshold for systemic therapy: Women with less than a 10% chance of relapse at 10 years are in the “low-risk” group and therefore would not routinely be considered candidates for systemic therapy. This change recognizes avoidance of relapse (as compared with survival) as a treatment goal and continues the trend of considering systemic therapy for women in increasingly better prognostic groups. Initially, adjuvant therapies were offered to lymph node-positive women who had a 30%–50% overall survival at 10 years (3). In 1988, the National Cancer Institute clinical alert extended the recommendation for adjuvant therapy to women with lymph node-negative breast cancer (4), a group with a 70% overall survival at 10 years. In 1995, the international consensus panel recommended that patients with a greater than 10% mortality at 10 years would be candidates for routine adjuvant systemic therapy (5). The current consensus panel lowered the threshold even further by suggesting systemic adjuvant therapy for patients with a greater than 10% risk of relapse (2). This shift toward a more inclusive treatment strategy may be resisted by some. However, it may be helpful to consider the scientific and social basis for these recommendations.

**Relapse-Free Survival Versus Overall Survival**

Freedom from disease is becoming a recognized treatment goal. This was evident during the deliberations by the Oncology Drug Advisory Committee (ODAC) to the U.S. Food and Drug Administration as its members considered tamoxifen as a potential chemopreventive. In a large U.S. study of 13,388 women, tamoxifen decreased the risk of invasive breast cancer by 49% at a median follow-up of 55 months (6). At this time point, however, there was no difference in mortality between the women on tamoxifen and those on placebo. Despite the absence of a benefit in mortality reduction, the ODAC voted to approve tamoxifen for reduction in breast cancer incidence.

**The Risk of Death in Early Breast Cancer Is Real and Significant**

Although there is a tendency to consider the relapse rate in the “good” and “intermediate” lymph node-negative prognostic groups to be small, the long-term survival impact may, in fact, be medically important. Examination of long-term follow-up data reveals that even the breast cancers in the best prognostic groups are associated with sizable disease-specific mortality. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has examined the disease-free survival of lymph node-negative patients who did not receive adjuvant systemic therapy according to tumor size (7). In their estrogen receptor (ER)-negative trial (B-13), the 5-year disease-free survival for untreated patients with tumors less than or equal to 1 cm in size was only 77%. In an ER-positive trial (B-14), the 5-year disease-free survival for patients with tumors of 1 cm or less in size was 82%. (It should be noted that the NSABP trials did not include patients with tumors of 1 cm or less in size that were detected only by mammography.) Rosen et al. (8) have also examined the long-term survival of women with lymph node-negative, T1 breast cancer who were treated by mastectomy from 1964 through 1970. Of 474 patients, 171 had a tumor size of less than or equal to 1 cm, and 303 patients had a tumor size of 1.1–2.0 cm. In women with a tumor size of 1 cm or less at 10 years of follow-up, 7% of the patients had died of breast cancer and 2% were alive with disease. By the end of 20 years, 10% of the patients had died of breast cancer and 2% were alive with disease. In women with tumors 1.1–2.0 cm at 10 years of follow-up, 18% of the patients had died of breast cancer and 4% were alive with disease. By the end of 20 years, 24% of the patients had died of breast cancer and 2% were alive with disease. Of interest, patients with tumor size of 1 cm or less tended to manifest more late recurrences than those with a tumor size of 1.1–2 cm. Twenty-five percent of the patients with tumor size 1 cm or less who developed a recurrence did so after the first 10 years of follow-up (years 10–21) compared with 16% of the patients with tumor size of 1.1–2.0 cm. Thus, in good- and intermediate-risk lymph node-negative breast cancers, the 20-year survival statistics are of concern. These long-term (20-year) survival statistics...
question the designation of good risk or intermediate risk in these lymph node-negative patients. Considered with the availability of effective therapies (see below), it is understandable that some physicians may offer such treatments to this subgroup of patients.

**Hormone Therapy**

A second change from the 1995 conference is the recommendation concerning hormonal therapy. The addition of tamoxifen to chemotherapy is now considered standard for premenopausal women with ER-positive, invasive tumors. Women with ER-negative tumors (even if >50 years of age), however, are unlikely to benefit from hormonal therapy, and, in this consensus statement, hormonal therapy is not recommended for postmenopausal women with hormone receptor-negative breast cancer. The 1995 Early Breast Cancer Trialists’ Working Group meta-analysis (9) provides the basis for this recommendation. In this study, 18,000 women with ER-positive tumors and 12,000 women with untested tumors (of whom an estimated 8000 would have been ER positive) treated with tamoxifen therapy demonstrated a 10.9% absolute survival benefit for women with lymph node-positive tumors and 5.6% absolute survival benefit for women with lymph node-negative breast cancer. The proportional reductions were similar for lymph node-positive and lymph node-negative breast cancer (47% reduction in recurrence and a 26% survival advantage in women treated with 5 years of tamoxifen at 10 years of follow-up). Benefits were observed irrespective of age, menopausal status, or chemotherapy.

**Extended Benefit of Chemotherapy**

A third change since the previous conference is the recommendation that the majority of patients be considered candidates for chemotherapy. This, perhaps, is potentially the most controversial of the recommendations. In 1995, chemotherapy was still under investigation for the largest subset of patients, postmenopausal, ER-positive women. In the 1998 consensus conference, chemotherapy is now an accepted practice option (Table 1). This change was due, in large part, to two important publications. In the 1995 *Lancet* overview of 18,000 women (10), polychemotherapy resulted in a statistically significant proportional reduction in recurrence (35% in women <50 years old and 20% in women ages 50–69 years). The corresponding reductions in overall mortality were 27% for women less than 50 years old and 11% for women 50–69 years of age. Polychemotherapy produced an absolute 10-year survival benefit of 7% for women with lymph node-negative disease and an 11% overall survival advantage for women with lymph node-positive breast cancer. The corresponding number for women ages 50–69 years are an absolute survival advantage of 2% in patients with lymph node-negative disease and 3% in women with lymph node-positive disease. Although women under 50 years of age derived more benefit from polychemotherapy than women ages 50–69 years, both groups of women experienced statistically significant benefit. Furthermore, the effects of chemotherapy were in addition to those derived from tamoxifen therapy. These overview results are also consistent with the results of the NSABP-B20 trial (11), in which women with lymph node-negative, ER-positive breast cancer who were treated with chemotherapy plus tamoxifen had a 5-year disease-free and overall survival advantage compared with women treated with tamoxifen alone. Thus, the 1998 St. Gallen’s consensus recommendations suggest that for the majority of women, chemotherapy would be considered an accepted treatment option. For patients with hormone receptor-positive disease, a combination of chemotherapy and hormonal therapy would be considered appropriate (Table 2).

Despite the absolute improvement in survival afforded by chemotherapy, there may be concerns that the 2%–3% absolute increment in survival for the ER-positive, lymph node-negative population is too small to be worth the discomfort of adjuvant treatment. Understanding this concern, the St. Gallen conference participants acknowledged the need to individualize therapy, based on physician judgment and patient preferences. Although physicians may be inherently conservative in the application of chemotherapy, many patients show a remarkable willingness to accept the increased risk of chemotherapy for improved survival.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Lymph node negative, minimal/low risk</th>
<th>Lymph node negative, intermediate risk</th>
<th>Lymph node negative or lymph node positive, high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>Lymph node negative, minimal/low risk</td>
<td>Lymph node negative, intermediate risk</td>
<td>Lymph node negative or lymph node positive, high risk</td>
</tr>
<tr>
<td>ER or PR positive</td>
<td>None versus tamoxifen†</td>
<td>None or tamoxifen†</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>ER or PR positive</td>
<td>None versus tamoxifen†</td>
<td>None or tamoxifen†</td>
<td>Tamoxifen ± chemotherapy†</td>
</tr>
<tr>
<td>Postmenopausal ER or PR positive</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Chemotherapy ± tamoxifen†</td>
</tr>
<tr>
<td>Postmenopausal ER and PR negative</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Chemotherapy + tamoxifen†</td>
</tr>
<tr>
<td>Elderly</td>
<td>None versus tamoxifen†</td>
<td>None or tamoxifen†</td>
<td>Chemotherapy ± tamoxifen†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

*Table 1. Changes in treatment recommendations from the 1995 and 1998 St. Gallen’s consensus conference for patients with primary breast cancer*

*Treatments that are considered accepted for routine use or baseline in clinical trials are in bold.

†Indicates treatments still being tested in randomized clinical trials. Italics indicate recommendations in 1998 that have changed since 1995. This includes treatments that were under investigation in 1995 that are now considered accepted by the panel. Since the recommendations for premenopausal, hormone receptor-negative patients have not changed, this subset is not represented in this table. ER = estrogen receptor; PR = progesterone receptor.
take potentially toxic treatments for small decrements in recurrence rate. According to a recent survey of 318 women who have received chemotherapy, the median improvement in the risk of breast cancer recurrence where adjuvant therapy would be accepted was 0.5%–1% (12). Thus, as recommended by the consensus panel, patient choice and clinical judgement will need to be considered in deciding chemotherapy for patients with lymph node-negative, ER-positive tumors.

WHERE DO WE NEED TO GO?

The effect of the 1998 St. Gallen consensus recommendations is to extend the acceptability of systemic chemotherapy to a wider range of breast cancer patients—to those with better prognosis, and specifically to those with postmenopausal, ER-positive disease. As the criteria for treatment become progressively more inclusive, the larger questions become the optimal selection of systemic therapies for individual subsets and the identification of a subset of patients where therapy could safely be withheld. For both questions, molecular markers for disease biology may play an increasingly important role in finding the solutions. Already, the conference participants have considered known clinical prognostic factors, such as hormonal status, pathologic grade, and young age of patient (<35 years old), in their stratification of lymph node-negative patients into good-, intermediate-, or high-risk groups. As noted in the St. Gallen consensus, the ER status is a major deciding factor in therapeutic selection. However, other biomarkers, such as proliferative fraction or HER-2/neu status, may have importance as well.

The Early Breast Trialists’ Working Group recent overview (10) highlighted the modest difference favoring anthracycline-based chemotherapy compared with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-like therapies. However, it is likely that only some patients benefit from the addition of anthracyclines to the adjuvant regimen. Emerging data suggest that the subset of lymph node-positive patients with tumors that overexpress HER-2 is likely to benefit from dose-intense anthracycline-based regimens. Retrospective analyses of two large randomized trials in women with lymph node-positive breast cancer (13,14) have suggested that patients with HER-2-positive tumors have an improved relapse-free and overall survival following dose-intensive anthracycline-based regimens compared with lower dose anthracyclines or non-anthracycline-containing regimens. These results are restricted to lymph node-positive patients and cannot be extrapolated to the lymph node-negative subsets. However, this possibility is intriguing and should be formally examined in the lymph node-negative setting.

Breast cancer is a disease with a long natural history, and the full impact of today’s research will not be fully realized for many years. Thus, the patterns of practice should be expected to change. The 1998 St. Gallen consensus conference produced a very reasonable set of recommendations based on clinical evidence and on the best judgment of experts in the field. Nevertheless, the scope of the changes, even when compared with 30 years ago, represents a substantial shift in philosophy. Given the speed of research today, we should expect no less in the next consensus meeting.

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Table 2. Current adjuvant treatment from the 1998 St. Gallen’s consensus conference for patients with primary breast cancer*

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Lymph node negative, minimal/low risk</th>
<th>Lymph node negative, intermediate risk</th>
<th>Lymph node negative, high risk or node positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER or PR positive</td>
<td>None or tamoxifen</td>
<td>Tamoxifen + chemotherapy</td>
<td>Chemotherapy + tamoxifen</td>
</tr>
<tr>
<td>ER and PR negative</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

*Treatments that are considered accepted for routine use or baseline in clinical trials are in bold. Considerations about a low relative risk of relapse, age, toxic effects, and socioeconomic implications on patient preference might justify the use of tamoxifen alone for ER- or PR-positive patients. ER = estrogen receptor; PR = progesterone receptor.