Interaction of Tamoxifen's Impact on Overall Net Mortality and Quality of Life

Review Article [1] | February 01, 1997
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Tamoxifen has well-documented activity in reducing breast cancer mortality. In addition, it has several secondary...

Introduction

The main objective of this article is to describe the effects of adjuvant tamoxifen (Nolvadex) on overall (net) mortality in patients surviving primary breast cancer, and in particular, to review the interactive relationship between the effects of tamoxifen on mortality and its effects on quality of life. Particular attention is paid to the issue of quality of life and its management, emphasizing that improvement of quality of life results in increased compliance, which, in turn, may improve the overall survival impact of tamoxifen. Quality of life represents an important, but not yet sufficiently explored consequence of tamoxifen therapy. Hence, a thorough and unbiased quantitative analysis of mortality outcomes is essential, as mortality reduction may drive parallel efforts to improve quality of life in order to ensure compliance.

Tamoxifen: Late Mortality in Breast Cancer Survivors

The estrogen agonistic and antagonistic effects of tamoxifen are well documented.[2] These actions of tamoxifen produce a range of benefits and side effects that may alter mortality from other conditions affecting breast cancer patients treated with tamoxifen. The changes in mortality may occur in opposing directions and vary in order of magnitude. Current evidence from several randomized trials demonstrates that tamoxifen reduces the incidence of contralateral breast cancer and decreases cardiovascular disease incidence and mortality with relative risk (RR) reductions of 0.5-0.8.[3-6] In contrast, uterine cancer and possibly thromboembolic episodes may result in excess deaths, with relative risk increases of 2-7.5 (Table 1).[4,7-9]

A recent British Columbia report[1] expressed the long-term impact of tamoxifen on the overall (net) mortality in breast cancer patients surviving their primary disease in quantitative terms taking into account all known tamoxifen-associated conditions that have the potential to affect late mortality. An attempt was made to integrate age-matched mortality rates of tamoxifen-associated conditions as they interact, in order to avoid a potential bias that could result if only one of the conditions was considered. Our calculations estimated that despite a projected modest increase in mortality from uterine cancer and thromboembolic episodes, there will be a more substantial mortality reduction due to avoidable deaths from contralateral breast cancer and cardiovascular events. These calculations were in addition to tamoxifen's previously confirmed improvement of breast cancer-specific survival, due to avoidance of locoregional and systemic relapses from primary breast cancer. Although recent reports of increases in the incidence of uterine cancer associated with tamoxifen usage [7,8] have captured the interest of the scientific community and media, our calculations show that there is only a moderate excess of deaths from endometrial cancer and that there is a more substantial reduction in deaths from contralateral breast cancer and cardiac events. One of the main conclusions of our integrated age-matched analysis is that the rather modest relative risk reductions for conditions such as contralateral breast cancer or cardiac events will result in large absolute numbers of saved lives, because the life-long underlying mortality rates for these conditions are high. On the other hand, using even very high relative risk increases for conditions such as uterine cancer or thromboembolic episodes results in a lower absolute number of excess deaths, because the underlying population mortality rates for these conditions are low. Because the mortality effects of different conditions are exerted in opposite directions, the overall
picture of tamoxifen's impact on long-term survival could be skewed if analyses are restricted to only one condition at a time. Thus, our methodology and results emphasize that only an integrated, age-matched analysis that captures all conditions simultaneously will have the potential to present an overall mortality picture and take into consideration all treatment-affected conditions. With this type of approach, the frequently observed unintentional or intentional reporting bias could be reduced or avoided.

**Tamoxifen and Quality of Life: General Comments**

While fear of uterine cancer is the most frequently cited reason for the reluctance of physicians and patients to consider tamoxifen therapy, it is the less well quantitated area of quality of life that constitutes the main problem with tamoxifen compliance. Tamoxifen-associated side effects range from hot flashes, vaginal dryness, and associated dyspareunia with reduced libido—the more typically described antiestrogen effects of tamoxifen—to much less frequently discussed, yet commonly observed complaints, such as insomnia, depression, ocular irritations, gastrointestinal symptomatology with nausea, and weight gain.

Although reported frequently in mild forms, the frequency of side effects of tamoxifen affecting quality of life is less well documented because quantification of quality of life is hampered by the subjective aspect of the complaints. The evaluation of quality of life is made more difficult because most clinicians do not use validated quality-of-life instruments consistently. Such instruments could provide reasonably objective evidence for the magnitude of effect on quality of life,[21,22] particularly if they were used more frequently and prospectively in tamoxifen studies, with testing of quality of life as a defined objective.

**Approaches Toward Improved Quality of Life**

Despite tamoxifen's definitively proven survival benefit, its adverse effects are sufficiently significant that they are an issue that needs to be addressed. Of particular importance is evidence that side effects affecting quality of life, which could be tolerated in patients with advanced or developed breast cancer, represent a large-scale problem in women who are otherwise well and who may be considering taking tamoxifen for breast cancer prevention.

From this perspective, it cannot be overemphasized that while the ultimate goal of therapy is overall improvement in survival, quality-of-life issues are of great importance, not only because of their impact on the mental health of patients, but also because noncompliance due to adverse events may prevent materialization of the survival gain, which is derived only if the medication is taken as prescribed. Therefore, if mortality is expected to decrease significantly, efforts to improve quality of life have to be escalated in proportion.

**Hormone Replacement Therapy**

The hot flashes and vaginal dryness, with related dyspareunia, loss of libido, and loss of energy, seen in a large number of patients taking tamoxifen, are clearly antiestrogenic effects. Although never tested prospectively, there is a reasonable expectation that these tamoxifen-associated menopausal complaints could be ameliorated by hormone replacement therapy (HRT) in the same fashion as are complaints associated with physiologic menopause.

According to many studies, the relative risk rates for the incidence of breast cancer in populations of women without breast cancer are only marginally increased by HRT.[10,11] Because of an associated benefit on nonbreast cancer events, HRT use has been advocated for routine therapy of menopausal symptoms or as means to improve overall longevity.[12] For similar reasons, the use of HRT in breast cancer survivors has been recently advocated for amelioration of menopausal symptoms resulting from adjuvant chemotherapy or tamoxifen that affect quality of life.[13,20] The use of HRT in breast cancer patients is particularly attractive if HRT is used under the protective umbrella of tamoxifen.[14] Preliminary evidence from small phase II studies of HRT even without tamoxifen indicates that the rate of breast cancer metastases may not be adversely affected by the use of HRT.[15-17] Furthermore, there are reasonable expectations that HRT use may not only improve quality of life in patients who suffer from adverse menopausal symptoms, but HRT may add to other protective effects of tamoxifen, such as effects on lipids or prevention of bone loss as it does in patients who do not have breast cancer.

On the negative side, thromboembolic episodes may be aggravated, and endometrial carcinogenesis remains a worrisome issue. Uterine cancer incidence could be substantially reduced with the use of
progesterone-containing HRT combinations due to the well-documented protective effect of progestins on the estrogen-mediated increase of endometrial neoplasia.[18] Because the addition of estrogen or progesterone may interfere with tamoxifen's effects on breast cancer, only very rigorous testing of their value in controlled clinical trials will fully confirm their overall benefit in tamoxifen-treated breast cancer patients. At least one randomized trial[19] and several proposals for HRT trials in breast cancer patients are presently under consideration by large centers or groups.[13,14] There has also been a call for studies to investigate the potential benefits of HRT treatment on menopausal side effects or quality of life, and also possibly on overall survival, in breast cancer patients treated with or without tamoxifen.[13,19,20]

Nonhormonal and Alternative Medicine Approaches

There is limited evidence for improvement of menopausal symptoms using nonhormonal and unconventional approaches. The best studied agents are alpha-adrenergic agonists, such as clonidine and lofexidine. (Clonidine is used in tablet form or as a transdermal patch.) For some patients, beta blockers such as propranolol have been used and anecdotal reports indicate a good outcome, although lightheadedness can be a problem. Tibolone is a steroid, with weak estrogenic, androgenic, and progestogenic activity, with no known adverse endometrial effects. Bellargal, a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital, is associated with improvement of hot flashes, although sedative effects, dry mouth, and vasoconstriction are possible side effects. The vitamin/herbal approaches include such agents as vitamin E, the Oriental or North American root of ginseng, primrose oil, and Astralagus. Vitamin E is considered effective by some women, particularly as it may relieve vaginal dryness. In most health food stores across North America, capsules or tea of ginseng are now available commercially. Ginseng has been used in China for centuries as a general, nonspecific stimulant and aphrodisiac and is also considered to be good for many health conditions, including menopausal symptoms. Its effect is made more credible by the fact that ginseng root is a rich source of phytoestrogens. Phytoestrogens, a class of phytosterols, are substances identified in plants that exert weak estrogenic effects with less well-documented stimulatory mitotic activity of pure estrogens. The higher intake of phytoestrogens in Asia is suspected to represent a common link to not only a lower breast cancer incidence in Asian countries, but also anecdotally with a reduced intensity of menopausal symptoms in women from underdeveloped countries. Primrose is an edible North American plant, and its seeds contain primrose oil, a nontoxic oil containing gamma-linoleic acid, the source of its alleged activity, which is considered to be of benefit in alleviating hot flashes. Astralagus, otherwise known as Huang Qi, is a root of a Chinese plant, one of the most popular components of Chinese herbal remedies considered to have multiple health benefits including improvement of hot flashes. Although these agents are used on a large scale in North America, data on the efficacy of these nonconventional approaches are strictly limited to anecdotal reports from individual women, greatly amplified by health food stores and holistic medicine lobbies. Thus, the issue of appropriate use of these agents clearly needs clarification and testing in properly designed controlled studies.

Exercise

Exercise and physical activity, perhaps by increasing serum and tissue levels of steroids, androgens, or endorphins, as well as by lowering blood pressure and reducing stress and headaches, may be an important step in relieving many symptoms of menopause, including side effects of tamoxifen, and improving quality of life. However, the influence of exercise and the biochemical processes mediating physical conditioning have been investigated only marginally, despite the fact that they have been frequently observed to be of major help in mediating subjective benefits on psychosocial trauma.

Conclusion

This report provides a review of tamoxifen's overall benefits and side effects, focusing on its impact on late mortality in breast cancer patients surviving their primary disease and on its interaction with a patient's quality of life during treatment. The discussion of tamoxifen's effect on late mortality focused on attempts to distinguish between individual versus total effects. While the survival improvement for primary breast cancer has been
firmly established, tamoxifen's full effect on late mortality in breast cancer survivors can be only estimated from quantitative reports of past tamoxifen trials of adjuvant therapy for breast cancer patients in which tamoxifen was also shown to affect the incidence and mortality rates of other conditions.

The evaluation of tamoxifen's effect on total mortality is complex, as relevant conditions are affected at different times, by different orders of magnitude, and frequently in opposite directions long after tamoxifen use. What is emerging, however, is that only an age-matched evaluation integrating all conditions affected by tamoxifen use will provide a complete picture of its real effect on overall mortality.

All side effects of tamoxifen, primarily those affecting quality of life, require prospective studies because their management is emerging as one of the most important aspects of obtaining higher compliance for tamoxifen therapy. Maximum survival benefit would be expected in a compliant population. Prospective testing of hormone replacement therapy is indicated, as evidence points toward enhanced quality of life and possibly improved survival compared with tamoxifen alone. The nonconventional approaches, similar to the entry of any new agents or approaches in oncology, also require controlled testing, on a scale perhaps even more rigorous than conventional therapies as their use is already advocated or practiced virtually without any attempt at outcome analysis. Because their side effects are generally minimal, the nonconventional approaches may have the potential to substantially improve quality of life relating to tamoxifen-associated or unassociated symptoms of menopause. They may thus contribute, in an unknown magnitude, toward a tamoxifen-mediated increase in late survival of breast cancer patients or populations of women using tamoxifen in prevention—a notion too important not to be tested prospectively.

References:


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