Adjuvant Therapy with Curative Intent: Is That Really So?

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Citation

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Abstract

To The Editor :

It is a mantra, a dogma, a belief system. It has merit. It has saved many lives. It is almost 50 years now since Bernie Fisher first noted the high relapse rate in patients with breast cancer who had been “cured” by surgery. He realized more needed to be done. He set up systemic studies, went step by step and established a new approach to the understanding and “early” breast cancer. Seventy years before that, Halstead had developed what was thought to be the best approach for the treatment of breast cancer. Based on the best thinking and understanding at that time, he developed a surgical method that helped many but also reduced the quality of life of many others without giving them any benefit – that is what we found out later.

The concept of adjuvant systemic therapy, now fifty years old, also needs to be looked at again. After fifty years, we are working with the same assumptions we started with. We are trying more aggressive adjuvant therapies in patients who may not have very aggressive disease. We are changing our clinical practice based on short term follow-up. We are accepting a 3-5% absolute risk reduction with some treatments based on a relative risk reduction is enough to satisfy an arbitrary statistical standard. We are reducing the quality of life of a 100 patients to possibly benefit 3, 4 or 5 of them. We are not even sure as to how many cures we are really achieving. When the patients are followed for 10-15 years we find that relapses occur in patients who were classified as having been cured at 5 years.

If a patient has a 50% risk of recurrence without treatment at 5 years and that risk can be reduced to 30% with moderately aggressive therapy that allows the patient to remain ambulatory and functioning, I would consider that to be worthwhile. However, if more aggressive therapy (added drugs, higher doses) reduces that risk to 27%, is it worthwhile? There is added toxicity, added costs and reduced quality of life and we help 3 patients. A hundred patients suffer to help 3! The argument of what “if you were one of those 3 patients” does not hold. It is a game of chance. A patient has a 80-90% chance of suffering from the extra side effects and 3% chance of being helped. At least that explanation should be given to the patient. Full disclosure should be provided rather than just stating that the more aggressive treatment is “better.”

When it comes to patients with node negative disease, adjuvant treatment is even less justified. If the less aggressive treatment reduces the risk of recurrence from 15% to 7% that seems justified both in absolute and relative terms. Adding more aggressive adjuvant treatments to get another 3-5% benefit does not seem justified. The issue becomes important when we consider that the data with these studies are available to 3-5 years. We know from the natural history of breast cancer that significant numbers of recurrences occur between 5 and 10 years after the diagnosis. It is one thing to do studies, but quite another to make such treatments the “standard” for management of early breast cancer.

Another point that needs to be taken into account is the availability of drugs that can be used to treat the recurrence. In the early years of NSABP and at the time when the principles and reasons for using systemic adjuvant therapy were enunciated, very few effective drugs were available. Remissions were short and there was no second or third line therapy. A lot has changed since the sixties, seventies and even the nineties. Effective drugs and combinations now allow a large number of patients with metastatic disease to have durable remissions and many options are available for subsequent relapses. It therefore makes good sense to treat patients in the early (adjuvant) phase of their disease with “reasonable” regimens that allow a good quality of life for the patient and result in significant reduction of risk of

recurrences. This would allow a hundred patients to suffer only a small degree of loss of quality of life. The small percentage who may relapse after this form of treatment will have many effective treatment options for their metastatic disease.

Why is this approach not being considered seriously is a question that perplexes me. I do have some ideas. As I said in the beginning, it is a mind set. The dogma is strong. It has been emphasized again and again that "the only way to cure breast cancer is to treat it before there are detectable metastases." Then there is the corollary "metastatic breast cancer cannot be cured." The "box" has been created. Thinking outside the box is unusual and may be dangerous given the fear of law suits. Physicians, unfortunately, are as likely as any other group to follow the rules, do what is the accepted standard. It took 70 years to challenge Halstead's dictum before modified radical mastectomy was considered to be an acceptable method of surgical treatment. In the 70's and 80's there was major objection to lumpectomy and radiation as an alternative to modified radical mastectomies. The equivalence of radical mastectomy, modified radical mastectomy and lumpectomy with radiation for local effectiveness could be demonstrated in a relatively short time and a change in practice was possible.

The demonstration of the benefits of less aggressive adjuvant therapy and treatment of the recurrences, if needed, will take longer. I realize that studies to demonstrate this would be difficult if not impossible to conduct.

There is another point to be made – unpleasant as it may be. Adjuvant systemic therapy and especially aggressive adjuvant systemic therapy is a major source of income for oncologists. For every patient with metastatic breast cancer, we probably have 8-10 patients on adjuvant therapy. Reducing this number would have a significant impact on the bottom line for oncologists, institutions and the pharmaceutical industry. Whether or not this dictates clinical practice is difficult to say but it may be a factor. I at least would like to see a critical review of the situation and would appreciate feedback from you all.

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References

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