Debatable Issues

DI-1. Chemotherapy: Is More Better?

DI-1-1 Yes

Karen H. Antman. *Columbia University, NYC, USA*

A relationship between dose and clinical response is well established in the laboratory. Women with metastatic breast cancer are essentially incurable with conventional dose therapy. Yet several high dose regimens yield complete response rates of 40 to 55% and a 15–20% unmaintained progression free survival at five years. Studies of women with > 10 involved lymph nodes report about a 65% relapse free survival at 3 to 4 years follow-up. One small South African randomized study in metastatic breast cancer reported a significantly improved survival and disease free survival for women treated with high dose chemotherapy.

Critical issues which need to be addressed include randomized trials in stage II, III and IV breast cancer, currently underway and multivariate analyses to determine which patients do not benefit from this approach. Since the majority of women with metastatic breast cancer continue to relapse despite dose intensive therapy, reasonable strategies to study include addition of other active agents, the use of two or more high dose treatments, immunological approaches to eliminate minimal residual disease, and gene therapy to introduce resistance to chemotherapy in hematopoietic progenitor cells. The role of involved hematopoietic stem cell grafts in relapse, and the optimal source of stem cells are also under study.

DI-1-2 No

Gabriel N. Hortobagyi. *University of Texas M.D. Anderson Cancer Center*

There are excellent reasons to test the hypothesis that dose-intensification (DI) of chemotherapy (CT) will lead to improved therapeutic efficacy. This hypothesis is based on preclinical data, retrospective analysis of clinical trials, and a few randomized clinical trials (RCT) within the standard dose ranges. This information suggests that higher DI of CT results in higher response rates (RR), and occasionally, in longer durations of response and overall survival (OS). Toxicity is also directly related to DI, both in terms of frequency and severity. Over the last 12 to 15 years the availability of modern hematopoietic support allowed the development of myeloablative CT as a safe and effective strategy against MBC. Combination high-dose CT in patients (pts) with refractory MBC results in high RR, and a very encouraging complete RR. However, most responses are transient, and no definite OS benefit has been documented. High-dose CT is used today in front-line therapy for MBC, either as induction and only treatment, or as consolidation of responses achieved with standard "induction" regimens. Both approaches have resulted in overall RR in 70% to 100% of pts and complete RR between 45% to 60%. Median remission durations after DI therapy ranged from 6 to 12 months, and several studies suggested that 15% to 25% of pts treated with high-dose CT remained progression-free beyond 3 years. However, high-dose CT programs require a marked selection process to ensure the maximum safety of the participants. In addition, only two small RCT have been reported. The results obtained with the DI arm in the first were, at best, similar to the results of standard-dose combination CT programs. The "standard-dose" arm of that trial had very poor results, considering that pts received no prior CT for MBC. In the second trial patients who achieved a CR were randomized to standard or high-dose CT. Those treated with high-dose had a reported longer time to progression, but a shorter survival than those treated with standard-dose CT. Therefore, at this time it is unknown whether the high complete RR, and the apparent 15% to 25% progression-free survival rate result from increased therapeutic efficacy, or simply reflect the extensive selection process. Ongoing prospective RCT will address this issue.

A similar situation exists for high-risk primary breast cancer (PBC). Small pilot studies of adjuvant high-dose CT suggested that short-term disease-free survival was superior to that obtained after standard adjuvant therapy. However, there is great variability in natural history of PBC, and the selection process for HDCT programs is extensive, and likely to exclude those pts at the highest risk of relapse. Therefore, while early results are encouraging, only completion of RCT can establish the role of these treatments as a reasonable alternative for patients with high-risk PBC.

DI-2. Screening, Yes or No?

DI-2-1 Yes

S. Ciatto. *Centro per lo Studio e la Prevenzione Oncologica, Firenze, Italia*

Evidence from controlled studies of the efficacy of mammographic screening suggests that screening by mammography may reduce significantly breast cancer mortality by about 30%, although this benefit has been proven so far only for women between the age of 50 to 69, and with organized screening programs run on a centralized basis by expert and full time involved operators.

The available evidence on screening efficacy justifies the recommendation by a variety of scientific societies and groups and by the European Community that screening should be offered on a population basis as a current policy, providing that proper organization, experience, and quality control is guaranteed.

No evidence is available to support the hypothesis that spontaneous screening, outside a centralized organized program, performed at existing mammographic practices will be of any benefit.

DI-2-2 No

C.J. Baines. *Department Preventive Medicine and Biostatistics, University of Toronto, 12 Queens Park Cres. W, Toronto, Canada M5S 1A8*

Simple answers to complex questions are usually wrong, so it would be foolish to say simply 'no' to screening. However before implementing screening it is essential not only to consider its direct and indirect costs and the magnitude of achievable benefits, but also to consider priorities vis a vis other health programs.

In women 50 and over the benefit of mammography screening is well established in spite of less than optimum imaging, single views and variable periodicity. Breast cancer mortality reduction is prompt and significant clinically and statistically.

In contrast, similar benefit in women under age 50 appears only eight or more years after initiation of screening, is less substantial than in older women and hovers around statistical significance.

The fact that more than a third of breast cancers in women who start screening in the 5th decade are detected in the 6th decade is unsettling. Also unsettling is the burden of anxiety, unnecessary procedures and even false positive cancer diagnoses women without breast cancer must endure.

While the dollar cost of breast screening is often expressed as being similar to that of a dialysis program in terms of life years saved, an indisputable difference is that no one in good health needs to undergo dialysis in order to help people with renal failure.

DI-3. Has Primary Chemotherapy a Routine Role?

DI-3-1 Yes

G. Bonadonna*, P. Valagussa. *Istituto Nazionale Tumori, Milano, Italy*

Primary chemotherapy followed by surgery and/or radiation is today emerging almost all over the world as a new approach for large but operable

breast cancers. Primary chemotherapy was initiated more than 20 years ago as part of the multidisciplinary treatment for patients presenting with stage III disease. Its aim was to achieve tumor shrinkage to facilitate irradiation or surgery, and both modalities were followed by additional (adjuvant) chemotherapy. Although in locally advanced breast cancer randomized studies comparing this strategy with a more classical approach consisting of local-regional modality followed by systemic therapy were lacking, there is now doubt that primary chemotherapy contributed to improve survival and became a standard treatment approach. The mounting interest for primary chemotherapy has resulted in an increasing number of studies performed in patients with operable breast cancer. From available reports of both randomized and non-randomized studies, the most immediate and recognized benefit of this new approach is primary tumor downstaging enabling to increase the frequency of breast-conserving procedures in women who are otherwise candidate for mastectomy. However, the main scope of primary chemotherapy is to further improve the continuous relapse-free survival through eradiation of distant micrometastases. Only a few randomized studies are so far available to answer this question and they have confirmed that primary chemotherapy is at least as effective as the more traditional approach of surgery followed by systemic treatment in high-risk patients. To conceive and operate a more radical departure from the traditional dogma, physicians should be encouraged to join current and future clinical trials.

DI-3-2 No

C.J.H. Van de Velde. *The Netherlands*

Abstract not available.