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Shulman, LN. Chemotherapy in the treatment of patients with metastatic breast cancer: high-dose, low-dose -- what have we accomplished? Am J Oncology Rev 1(3):169-70, 2002

Commentary by Lawrence N. Shulman, M.D., Vice Chair for Clinical Services/Adult Oncology, Dana-Farber Cancer Institute (Harvard Medical School), Boston.

"The article by Berry and colleagues represents the results of nearly 30 years of clinical investigation in the treatment of patients with metastatic breast cancer. The results are not encouraging[1]...the seminal message is that neither [standard or high dose chemotherapy] has done a great deal to improve the outcome of patients with this disease."

"[over the past 20 years]... We relentlessly combined chemotherapy agents in various regimens, with ever-increasing dose intensity...as seen in this compilation of data, the survival for patients participating in these studies is exactly the same, less than 2 years. These four studies are a snapshot of hundreds of studies done throughout the world, spanning 30 years, utilizing innumerable combinations of standard dose chemotherapy without a hint of significantly improved survival."

Shulman noted that a retrospective comparison[1] of the above, well-characterized "standard dose" database with a less well characterized "high dose" database suggested that there was increased early mortality for high dose therapy (not surprising), while **"the difficult aspect of this manuscript to accept is the somewhat uncertain conclusion of the long term benefit from high-dose therapy...there appears to be a small number of patients who have long-term survival after high dose therapy...the concept that *highly selected* patients whose tumors are responsive to chemotherapy can have long-term remissions from standard dose chemotherapy as well is supported by a [different] retrospective study[2]."**

"The one large [prospective] **randomized trial....showed no difference in survival for patients treated with standard-dose versus high-dose chemotherapy. The median survival for both groups was 2 years, and no subset of patients seemed to benefit from high dose therapy.[3]"**

"Even if one were an optimist and concluded that the [high dose] data suggested that a small but significant subgroup of patients benefited from this approach, one must remember that the patients participating in these studies are already highly selected for age, performance status, response to induction therapy, and other factors, and that...at best we must be helping only an incredibly small percentage of the patients with this disease."

"Clearly, more effective therapies are desperately needed for women with metastatic breast cancer, and after 30 years of investigation aimed at intensified multiagent chemotherapy we should look for other avenues of study."

"[noted breast cancer oncologist] Powles...concluded[4] that chemotherapy had not changed overall survival, which was approximately 2 years prior to the use of chemotherapy and afterward. This is the same survival seen in the studies outlined in [the present] manuscript.... [Powles concluded] the fact that regressions of breast cancer had no influence on overall survival must reflect the inadequacy of present-day chemotherapy. Powles published his manuscript in 1980. One could say the same applies in 2002."

"Powles wonders how the use of chemotherapy , which clearly induces responses in some patients, cannot have affected the overall survival. *Does chemotherapy shorten survival of some patients, while prolonging the survival of others*?"

In other words, "standard" (one size fits all) chemotherapy of metastatic breast cancer is a zero sum game.

References:

[1]: J Clin Oncol 2002 Feb 1;20(3):743-50 *High-dose versus standard chemotherapy in metastatic breast cancer: comparison of Cancer and Leukemia Group B trials with data from the Autologous Blood and Marrow Transplant Registry.* Berry DA, Broadwater G, Klein JP, Antman K, Aisner J, Bitran J, Costanza M, Freytes CO, Stadtmauer E, Gale RP, Henderson IC, Lazarus HM, McCarthy PL Jr, Norton L, Parnes H, Pecora A, Perry MC, Rowlings P, Spitzer G, Horowitz MM. University of Texas M.D. Anderson Cancer Center, Houston, 77030, USA. dberry@odin.mdacc.tmc.edu

Abstract: PURPOSE: To assess survival of patients with metastatic breast cancer treated with high dose chemotherapy (HDC) versus standard-dose chemotherapy (SDC).

PATIENTS AND METHODS: SDC in four Cancer and Leukemia Group B (CALGB) trials was compared with hematopoietic stem-cell support in patients from the Autologous Blood and Marrow Transplant Registry. Cox proportional hazard regression incorporated potentially confounding effects. A total of 1,509 women were enrolled onto CALGB trials, and 1,188 women received HDC. No significant survival differences existed by CALGB trial or HDC regimen. Consideration was restricted to candidates for both SDC and HDC. The resulting sample included 635 SDC and 441 HDC patients. The outcome of interest was overall survival.

RESULTS: The HDC group displayed better performance status. The SDC group had slightly better survival in first year after treatment. The HDC group had lower hazard of death from years 1 to 4 and had somewhat higher probability of 5-year survival (adjusted probabilities [95% confidence intervals], 23% [17% to 29%] v 15% [11% to 19%], P =.03).

CONCLUSION: After controlling for known prognostic factors in this nonrandomized analysis of two large independent data sets, women receiving HDC versus SDC for metastatic breast cancer have a similar short-term probability of survival, and might have a modestly higher long-term probability of survival.

[2]: J Clin Oncol 1997 Oct;15(10):3171-7 Comment in: J Clin Oncol. 1997 Oct;15(10):3169-70. J Clin Oncol. 1998 Mar;16(3):1238-9. *Impact of selection process on response rate and long-term survival of potential high-dose chemotherapy candidates treated with standard-dose doxorubicin-containing chemotherapy in patients with metastatic breast cancer.* Rahman ZU, Frye DK, Buzdar AU, Smith TL, Asmar L, Champlin RE, Hortobagyi GN. Department of Breast Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA. zrahman@notes.mdacc.tmc.edu

Abstract: PURPOSE: Most of the data about high-dose chemotherapy (HDCT) for metastatic breast cancer are derived from phase II studies. The interpretation of these data depends on comparisons with data from properly selected historical control patients treated with standard therapy under similar circumstances. We report the long-term results of patients with metastatic breast cancer who were eligible for HDCT but were treated with doxorubicin-containing standard-dose chemotherapy.

PATIENTS AND METHODS: Prospectively collected data from 18 successive doxorubicin-containing protocols for the treatment of metastatic breast cancer were evaluated. Using common eligibility criteria for HDCT, we identified patients who would have been candidates for HDCT. We analyzed response rates, progression-free survival (PFS), and overall survival (OS) for all patients, potential HDCT candidates, and noncandidates.

RESULTS: A total of 1,581 patients was enrolled onto the 18 studies. Six hundred forty-five were HDCT candidates, and 936 were noncandidates. The complete response rate was 27%

for HDCT candidates and 7% for noncandidates; median PFS was 16 and 8 months and median OS was 30 and 17 months, respectively. Survival rates for HDCT candidates and noncandidates, respectively, were 21% and 6% at 5 years and 7% and 2% at 10 years.

CONCLUSION: This study suggests that encouraging results of single-arm trials of HDCT could partially be due to selection of patients with better prognoses and further stresses the importance of completing ongoing randomized trials of HDCT to assess the relative efficacy of HDCT in patients with metastatic breast cancer.

[3]: N Engl J Med 2000 Apr 13;342(15):1069-76 Comment in: N Engl J Med. 2000 Apr 13;342(15):1119-20. N Engl J Med. 2000 Aug 10;343(6):439-40; discussion 440-1. N Engl J Med. 2000 Aug 10;343(6):439; discussion 440-1. N Engl J Med. 2000 Aug 10;343(6):440; discussion 440-1. *Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer.* Philadelphia Bone Marrow Transplant Group. Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN, Brodsky I, Martino S, Lazarus HM, Erban JK, Sickles C, Glick JH. Bone Marrow and Stem Cell Transplant Program, University of Pennsylvania Cancer Center, Philadelphia 19104, USA. stadtmau@mail.med.upenn.edu

Abstract: BACKGROUND: We conducted a randomized trial in which we compared high-dose chemotherapy plus hematopoietic stem-cell rescue with a prolonged course of monthly conventional-dose chemotherapy in women with metastatic breast cancer.

METHODS: Women 18 to 60 years of age who had metastatic breast cancer received four to six cycles of standard combination chemotherapy. Patients who had a complete or partial response to induction chemotherapy were then randomly assigned to receive either a single course of high doses of carboplatin, thiotepa, and cyclophosphamide plus transplantation of autologous hematopoietic stem cells or up to 24 cycles of cyclophosphamide, methotrexate, and fluorouracil in conventional doses. The primary end point was survival.

RESULTS: The median follow-up was 37 months. Of 553 patients who enrolled in the study, 58 had a complete response to induction chemotherapy and 252 had a partial response. Of these, 110 patients were assigned to receive high-dose chemotherapy plus hematopoietic stem cells and 89 were assigned to receive conventional-dose chemotherapy. In an intention-to-treat analysis, we found no significant difference in survival overall at three years between the two treatment groups (32 percent in the transplantation group and 38 percent in the conventional-chemotherapy group). There was no significant difference between the two treatments in the median time to progression of the disease (9.6 months for high-dose chemotherapy plus hematopoietic stem cells and 9.0 months for conventional-dose chemotherapy).

CONCLUSIONS: As compared with maintenance chemotherapy in conventional doses, high-dose chemotherapy plus autologous stem-cell transplantation soon after the induction of a complete or partial remission with conventional-dose chemotherapy does not improve survival in women with metastatic breast cancer.

[4]: Lancet 1980 Mar 15;1(8168 Pt 1):580-2 *Failure of chemotherapy to prolong survival in a group of patients with metastatic breast cancer.* Powles TJ, Coombes RC, Smith IE, Jones JM, Ford HT, Gazet JC.

Abstract: Overall survival of patients with primary breast cancer has not improved in the past ten years, despite increasing use of multiple-drug chemotherapy for treatment of metastases. Furthermore, there has been no improvement in survival from first metastasis, and **survival may even have been shortened in some patients given chemotherapy.**