Lesson learned from high-dose chemotherapy for high-risk breast cancer (What you see is what you mean)

Recognition of the importance of receptor expression is crucial for understanding treatment effects in the adjuvant treatment of breast cancer. The Netherlands Working Party on Autologous Transplantation in Solid Tumors recently presented the results of a randomized study comparing conventional dose chemotherapy with conventional dose chemotherapy followed by high-dose chemotherapy [1]. The authors should be complimented for providing data after a proper duration of follow-up and for having dissected them in a way that provides the readership with hypotheses-generating information [2]. The study was designed in an era when adjuvant therapies were prescribed according to risk factors: the higher the risk the more intensive the treatment. Recent developments include an increasing attention to predictive factors and to systemic therapies prescribed according to the higher chance of response [3]. As presented by the Dutch investigators, response to higher dose chemotherapy for patients who are at high risk for relapse is associated with some very interesting and unpredicted features: benefit was seen almost exclusively in patients with low grade breast cancer, in patients at young age (<40 years), and in those who had no overexpression of HER2/neu in their primary tumor. Furthermore, the patterns of response in this latter subpopulation are similar to those observed with endocrine treatments (i.e. delayed onset of the treatment difference).

The interpretation of these data might be facilitated by the following information:

- In a series of 4565 consecutive patients, all operated on at the European Institute of Oncology from September 1999 to December 2002, 864 (18.9%) had HER2/neu overexpression classified as 3+, while 3701 patients (81.1%) had either 0 (58.3%), 1+ (11.0%) or 2+ (11.8%) classified tumors (Table 1). The table shows the correlation between the degree of expression of estrogen and progesterone receptors separately for pre- and postmenopausal women, clearly indicating the higher prevalence of endocrine responsive disease in the group of patients selected by the exclusion of HER2/neu overexpression. It is noteworthy that patients of premenopausal age with endocrine responsive disease are more likely to achieve a large endocrine effect with the high dose chemotherapy regimen through ovarian function suppression. Also women of postmenopausal age may obtain some additional endocrine effect from suppression of adrenals [4] due to cytotoxics and steroids, both given at higher doses to patients in the group allocated to high-dose chemotherapy.

- The International Breast Cancer Study Group (IBCSG) Trial 15-95 of high-dose chemotherapy given up front for three courses compared with conventional dose regimen in 344 patients [5] also showed that high-dose chemotherapy was effective primarily in a subgroup of young women (<40 years of age). This was a retrospective analysis and therefore should be considered with caution. Endocrine effects of chemotherapy were recorded and in the high-dose group 85% of 95 patients with known menstrual activity had amenorrhea compared with only 48% of 98 patients in the conventional dose group. We therefore conclude that intensive chemotherapy should be studied in a population of patients with tumors that are not endocrine responsive to avoid the endocrine-related confounding effect.

Table 1. Correlation between HER2/neu overexpression and degree of expression of ER and PgR

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>ER and PgR expression</th>
<th>HER2/neu 3+, n (%)</th>
<th>HER2/neu 0 or 1+, 2+, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>ER and PgR &lt;10%</td>
<td>132 (38.3)</td>
<td>213 (61.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ER or PgR &lt;10%</td>
<td>234 (43.7)</td>
<td>301 (56.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>ER and PgR ≥10%</td>
<td>63 (23.3)</td>
<td>207 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>ER or PgR &lt;10%</td>
<td>141 (20.9)</td>
<td>533 (79.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>ER and PgR ≥10%</td>
<td>169 (13.7)</td>
<td>1066 (86.3)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>ER and PgR ≥10%</td>
<td>125 (8.3)</td>
<td>1381 (91.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*In number of cells.
ER, estrogen receptor; PgR, progesterone receptor.
Postoperative chemoradiotherapy after curative gastrectomy for cancer

I read with interest the paper by Park et al. on postoperative chemoradiotherapy for gastric cancer, published in a recent issue of *Annals of Oncology* [1] and I fully agree with the conclusions they report in the Discussion.

In particular, I share the perplexity of the authors in extrapolating the benefit of chemoradiotherapy achieved in the patients undergoing a limited lymphadenectomy in the Intergroup trial INT-0116 [2] also to those undergoing D2 lymph node dissection. In fact, patients in the American trial would be considered undertreated according to the surgical standard of many centers in Europe and Japan and this could account for the success of the subsequent chemoradiotherapy.

In support to this thesis, it is interesting to note that the 5-year survival of the 290 patients in the Korean study [1] who received adjuvant chemoradiotherapy is quite comparable, stage by stage, to that of 618 patients enrolled in an Italian randomised study comparing subtotal versus total gastrectomy alone, both procedures being associated with D2 lymph node dissection [3]. Namely, the 5-year survival for stages IB, II, III and IV were 93%, 75%, 53% and 13% in the Korean study versus 86%, 75%, 61% and 13% in the Italian study, respectively.

Although such comparisons should always be viewed with caution, I am asking whether it is ethically correct to compare, in a randomized fashion, a D2 gastrectomy with a D2 gastrectomy plus adjuvant chemotherapy if the expected clinical benefit is so limited and this adjuvant treatment appears to be a demanding procedure and is sometimes toxic for the patient. Moreover, I wonder how big the sample size should be if the difference to be detected between the two groups is very small!

I acknowledge that randomized clinical trials are the best way to proceed on the road of evidence-based medicine; nevertheless, surgeons and medical oncologists should realistically consider that the extent of lymphadenectomy makes some difference to the outcome of patients who undergo surgical treatment for cancer of the stomach [4].

F. Bozzetti
Istituto Nazionale Tumori, Milan, Italy (*E-mail: dottfb@tin.it)

References


DOI: 10.1093/annonc/mdh055