The Treatment of Individual Patients Is More Than a Trial

Alberto Bottini, Alfredo Berruti, Daniele Generali, Luigi Dogliotti

Correspondence to: Alberto Bottini, MD, Unità di Patologia Mammaria, Azienda Ospedaliera Istituti Ospitalieri, Viale Concordia 1, Cremona 26100, Italy (e-mail: alberto.bottini@email.it).

The use of chemotherapy before surgery (neoadjuvant or preoperative approach) is the standard of care in patients with locally advanced and inflammatory breast cancer because a clinical and/or radiological response is achieved in most patients, facilitating optimal surgery and radiation therapy. The success of neoadjuvant chemotherapy for locally advanced breast cancer led to studies investigating this treatment approach among women with operable breast cancer (primary chemotherapy).

Many years have gone by since primary/neoadjuvant chemotheraphy was first introduced by Gianni Bonadonna in the management of operable breast carcinoma (1), and the National Surgical Adjuvant Breast and Bowel Project-B18 multicenter randomized trial demonstrated the similar therapeutic value between primary and adjuvant treatments (2).

Subsequent randomized clinical trials and a meta-analysis of adjuvant vs primary chemotherapy in patients with early-stage operable breast cancer (3) showed no difference in disease-free or overall survival rates.

On these bases, if a patient with operable breast cancer is candidate to a systemic therapy on the basis of presurgical, clinical, and immunohistohemical evaluation, this treatment can be administered either in the neoadjuvant or adjuvant setting.

The primary systemic therapy (PST) strategy implies an up-front systemic therapy: chemotherapy ± molecular target agents or endocrine therapy followed after 4–6 months by surgery and subsequent adjuvant therapy if needed (ie, endocrine therapy in estrogen receptor–positive tumors).

Potential advantages of the PST approach include tumor downstaging increasing the rates of breast conservation and the possibility of monitoring tumor response. Adjuvant therapy, in fact, is a blind approach, whereas PST can test in vivo the sensitivity of cancer cells to the systemic therapy used, offering the opportunity to obtain information of treatment efficacy in any treated patients.

These issues notwithstanding, PST are rarely used in clinical routines because in case of operable primary breast cancer, most clinicians usually prefer to adopt surgery followed by adjuvant therapy.

Many reasons may justify this approach: 1) there is no formal demonstration that disease response is a surrogate parameter of efficacy; 2) the real advantage of monitoring tumor response during PST is the opportunity to adjust, tailor, individual treatment on the basis of the initial tumor response obtained; however, no prospective trials have demonstrated the efficacy of this approach; 3) perhaps most importantly, the patient frequently prefers the rapid removal of her tumor because the delay in surgical approach can be a cause of anxiety.

The identification of patient subsets in which PST may be superior to adjuvant therapy and the validation of surrogate parameters of treatment efficacy are crucial steps toward the implementation of PST in clinical practice (4).

Beside its employment in clinical routine, PST is increasingly popular in terms of research perspective where it has an irreplaceable role in the early clinical investigation of new biological drugs. PST studies are extremely useful in translational research to study the impact of systemic treatment on tumor biology in vivo, to assess potential predictive factors, and to allow pharmacodynamic and pharmacogenetic substudies. They may also be very informative in testing synergies of new associations. Furthermore, a new type of translational research has been recently developed for more frequent smaller tumors. In the “biological window” design (5), very similar to a phase 0 trial, the aim is not to downstage surgery, but to make use of the elapsed time between diagnostic biopsy and surgical resection to give new molecular target agents to carry out information on their biological activity.

Future clinical trials of PST should be designed with molecular subsets of breast cancer in mind. As previously mentioned, whether tailoring individual treatment according to response to PST is really beneficial for patients still remains to be demonstrated but assessing such a strategy will be facilitated in the near future thanks to functional and molecular imaging that can further improve early assessment of tumor response, and, above all, the development of newer therapies, such as antiangiogenic therapies or DNA repair targeting drugs, with the anticipated absence of cross-resistance with anthracyclines and taxanes. Furthermore, molecular analyses of post-chemotherapy surgical residual disease for proliferative factors and predictive factors may also be very informative in the future to select the most appropriate adjuvant treatment.

On these bases, PST is destined to be increasingly adopted in the management of operable breast cancer, but this approach has ethical implications because communication and informed consent from patients supervene in different settings when considering, on the one hand, patients still bearing the primary cancer in their breast tissue and, on the other one, patients without.

This underlines the importance of breast units as experienced multidisciplinary teams composed of dedicated professional figures such as breast surgeons, breast oncologists, breast pathologists, geneticists, radiotherapists, psychologists, palliative care specialists, etc (6). Their purpose is to give to breast cancer patients the advantages of the expertise of a multidisciplinary team working together to decide the best ways to treat the disease and offer the best communicative approach.
In addition, the increasing complexity of new trial designs need experienced and well-organized teams of clinical and biological scientists. We believe that breast units, as already described, could offer the best organization model for administering PST.

The third International Symposium of PST was held in Cremona, Italy, in September 2010 with the aim to review state-of-the-art scientific evidence and expert opinions on this approach. The workshop brought together laboratory and clinical scientists to cross-fertilize and catalyze research on this important therapeutic approach.

We have had the privilege of assembling these proceedings to convey the workshop highlights for the interested scientific community.

This important meeting underlined that PST is a useful tool for the management of early breast cancer in clinical routines, and preoperative trials are among the most exciting areas of cancer research.

References


Funding


Affiliations of authors: Unità di Patologia Mammaria, Azienda Ospedaliera Istituti Ospitalieri, Cremona, Italy (ABo, DG); Oncologia Medica, Dipartimento di Scienze Cliniche e Biologiche, Azienda Ospedaliera Universitaria San Luigi, Orbassano, Italy (ABe, LD).