Primary Systemic Therapy in Breast Cancer

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Key Words

Systemic therapy, primary · Neoadjuvant therapy · Breast cancer · AGO

Summary

Initially, only patients with inflammatory or inoperable locally advanced breast cancer were candidates for preoperative chemotherapy. The aim was to downstage tumors to make a surgical procedure feasible. Currently, preoperative therapy is administered to an increasing number of patients. The monitoring of the treatment serves as an in vivo test. The prognosis of patients is the same as with adjuvant therapy. The rate of pathologically complete remission is increasing with more experience with the neoadjuvant treatment. New drugs contributed to the development of such treatment strategies.

Schlüsselwörter

Systemische Therapie, primäre · Neoadjuvante Therapie · Mammakarzinom · AGO

Zusammenfassung

Die präoperative Therapie wurde ursprünglich zur Besserung der Operabilität eingesetzt. Bei inoperablen Tumoren konnte eine chirurgische Intervention angeschlossen werden, und bei initial sehr großen Karzinomen konnte durch den Einsatz der präoperativen Therapie eine brusterhaltende Therapie durchgeführt werden. Heutzutage wird die präoperative Therapie immer häufiger eingesetzt. Neben der Erhöhung der Rate brusterhaltender Operationen kann das Therapieansprechen wie ein in-vivo Sensibilitätstest gewertet werden. Die Prognose der Patientinnen ist mindestens so gut wie nach adjuvanter Therapie. Die Rate an pathologisch kompletten Remissionen erhöhte sich mit zunehmender Erfahrung mit dieser Therapiemodalität. Die Einführung neuer Medikamente führt auch zu einer Verbesserung der Strategiekonzepte beim Mammakarzinom.

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The cornerstone for the use of primary chemotherapy for the treatment of breast cancer has been laid in the early 1970s. The NSABP-B18 study compared an anthracycline regimen (AC×4, q3w) that was given either before or after surgical therapy. The study originally intended to show the superiority of one of the regimens, but long-term results demonstrated identical survival rates of the two groups [1]. Further clinical studies confirmed a comparable efficacy of both neoadjuvant

and adjuvant chemotherapy protocols. Protocols that need to be mentioned besides the NSABP-B18 study (AC×4, n = 1523) are the French study (FAC×4, n = 390), the EORTC (FEC×4, n = 698), the ECTO (AT-CMF, n = 13) and the NSABP-B27- (FEC×4, n = 2411) study [2–5]. In their meta-analysis Mauri et al. [6] summarized 9 important randomized studies and outlined advantages and disadvantages of both preoperative and postoperative chemotherapy regimes. No significant differences concerning survival (RR = 1.00, 95% confidence interval (CI) = 0.90–1.12), tumor progression (RR = 0.99, 95% CI = 0.91–1.07) or development of metastases (RR = 0.94, 95% CI = 0.83–1.06) could be seen. Primary systemic therapy, however, was associated with an increased rate of local relapses (RR = 1.53, 95% CI = 1.11–2.1). The rate of clinical complete remission varied between 7 and 65% (p < 0.001), pathological complete remissions were described between 4 and 29% (p < 0.001). Response to therapy described by pathological complete remission (pCR) in breast and/or axilla correlates with better survival [1, 6–9].

Data confirming advantages of neoadjuvant treatment for patients with primary inoperable disease have been published, demonstrating an increased rate of breast-conserving surgery for these patients [1–3, 5, 10–13]. An additional advantage of neoadjuvant chemotherapy is rooted in the possibility of measuring clinical response at an early stage of disease – also leading to a major psychological advantage for the patient. Switching chemotherapeutic agents towards non cross-resistant regimes is possible, allowing fast evaluation of new drugs and/or therapeutic modalities [1, 14].

Primary inoperable invasive carcinomas (LOE 1c / A, AGO ++), inflammatory breast cancer (LOE 1b / B, AGO ++) and established indications for the need of postoperative chemotherapeutic treatments (LOE 1b / A, AGO +) represent indications for primary systemic therapies [1–2, 10–15] (fig. 1). If a priori any contraindication against breast conserving therapy can be determined (e.g. multicentric carcinoma, wide areas of microcalcifications or in case radiotherapy is not feasible, each LOE V / D, AGO ++), then primary systemic therapy can not be used in the intention to conserve the breast in the following surgical procedure [16]. Chemotherapeutic combinations described in established clinical studies should be applied when determining therapeutic regimes, referring mainly to AC-D (LOE 2b / A, AGO +), DAC (LOE 2b / B, AGO +), and AP-CMF (2b/B, AGO +) [4–5, 13, 17] (fig. 2).

In HER2/neu-positive tumors trastuzumab has been employed as primary systemic therapy [18–20]. In 2005 Buzdar and coworkers [18] were able to show significantly increased pathological complete remission rates when trastuzumab was added to a regimen with paclitaxel ×4, q3w followed by FEC ×4 q3w (25% vs. 66.7%). Already after 32 patients had been randomized, the Data Monitoring Committee stopped the study. At present, trastuzumab is used in HER2/neu-positive patients undergoing primary systemic therapy in clinical study conditions (e.g. GEPARQUATTRO, HEDON). The out-of-

	Oxford LOE	AGO GR
> Primary inoperable invasive breast cancer	1c	A ++
> Inflammatory breast cancer	1b	B ++
> Clear indication for similar postop. CT given	1b	A +*

* Study participation recommended

Fig. 1. Indications for primary systemic chemotherapy.

	Oxford LOE	AGO GR
> AC → D	2b	A +
> DAC	2b	B +
> AP-CMF	2b	B +
> P weekly → FAC	2b	B +/-
> Dose-Dense E → P	2b*	B +/-

AGO-recommendation reflects treatment efficacy in the adjuvant setting

D = Docetaxel; P = Paclitaxel

Fig. 2. Recommended protocols for primary systemic chemotherapy.

	Oxford LOE	AGO GR
> + Trastuzumab neoadjuvant	2b	C +*
> + Trastuzumab adjuvant	2b	B ++*

* Study participation recommended

Fig. 3. Recommendations for primary systemic therapy in HER2-positive tumors.

study use of trastuzumab is not part of clinical routine yet (fig. 3).

Primary Systemic Therapy Surgical Procedures			
	Oxford LOE	AGO GR	
➤ Precise documentation of tumor location before, during and at the end of PST	5	D	++
➤ Surgery after PST	2b	C	++
➤ Microscopically clear margins	5	D	++
➤ Excision within new margins	3b	C	+
➤ Sentinel node biopsy (before or after)	2b	B	+/-*
* Study participation recommended			

Fig. 4. Recommendations for surgical procedures after primary systemic therapy.

Compared to primary surgical therapy the implementation of primary systemic therapy holds a number of risks (fig. 4). Localization of the tumor needs to be defined and precisely described, response to therapy needs to be monitored at regular intervals (LOE 5 / D, AGO ++). Surgery after PST is obligatory (LOE 2b / C, AGO ++) and should be scheduled about 2–4 weeks after the last cycle of chemotherapy and after passing the leucopenic nadir (LEO 4/ C, AGO ++). A reliable/assured microscopic complete resection must be reached (LOE 5 / D, AGO ++). If this condition is met, excision may be conducted in the new (= after PST) tumor boundaries (LOE 3b/ C, AGO ++). No stringent data exist concerning sentinel node biopsy before or after PST. The NSABP-B27 study examined this issue systematically and showed results according to the established approach. Sentinel node biopsy in combination with PST should – at present – be limited to clinical studies (LOE 2b / B, AGO +/-) [5, 14, 22].

Indication for radiation therapy needs to be determined before PST according to generally valid standards. Therefore, radiation after mastectomy is indicated when a patient shows positive lymph nodes or T3/T4 tumors (cN+, cT3/4a-d). Radiation therapy should begin 2–3 weeks after surgery (LOE 2b / B, AGO ++).

In case of no response to primary systemic therapy, i.e. no change in the tumor evaluation, chemotherapy should be completed and surgery should follow as it has been originally

Primary Systemic Therapy Procedures In Case Of Insufficient Response			
	Oxford LOE	AGO GR	
In case of stable disease:			
➤ Completion of PST, followed by surgery	5	D	++
➤ Continuation of PST with non cross-resistant regimen	2b	B	+
➤ AC X 4 → D X 4			+
➤ DAC X 2 → NX X 4			+/-
In case of progressive disease:			
➤ Stop of PST and immediate surgery or radiotherapy	5	D	+++
➤ Additional adjuvant chemotherapy	4	D	+/-
* Study participation recommended			

Fig. 5. Recommendations for primary systemic therapy in case of insufficient response.

planned (LOE 5 / D, AGO ++). Alternatively, therapy can be switched to a non cross resistant regime (LOE 2b / B: AC x4 switch to D x4, AGO +; DAC x2 switch to NX x4, AGO +/-). If the disease is progressive under therapy, PST has to be abandoned and surgery or radiotherapy must follow immediately (LOE 5 / D, AGO ++). Concerning adoption of an additional adjuvant therapy no reliable data exist (LOE 4 / D, AGO +/-) [13–14, 23] (fig. 5).

At present, no long-term results exist comparing primary systemic to primary endocrine therapy. Ideal duration of therapy is unclear. This leads to only general recommendations: Primary endocrine therapy is indicated for postmenopausal patients with hormone sensitive breast tumors who are not able to undergo chemotherapy or who show inoperable disease (LOE 5 / D, AGO +). Study results demonstrate that the use of aromatase inhibitors (>3 months instead of tamoxifen) leads to an increased rate of breast conserving therapy (LOE 1b / B, AGO +/-). A concurrent chemo-endocrine therapeutic regime in primary application is obsolete (LOE 1b / A, AGO --) [24–29]. Present review articles [14, 30] look intelligently into the topic ‘primary systemic therapy’ and confirm it as a standard therapeutic option in the treatment of primary breast cancer. An increased rate of breast conserving therapy is classified as an essential clinical advantage. Therefore, pathological complete remission is considered a surrogate marker for the efficacy of chemotherapeutic regimens.

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