

Intra-arterial Chemotherapy: A Safe Treatment for Elderly Patients with Locally Advanced Breast Cancer

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Abstract. *The feasibility, toxicity and local response rates of intra-arterial chemotherapy with 5-fluorouracil, epirubicin and mitomycin in patients over 75 years with locally advanced breast cancer was evaluated. Patients and Methods: Ten patients were treated by the transfemoral Seldinger technique, with the catheter tip placed into the internal mammary artery. In order to evaluate the vessels perfusing the tumor, blue dye solution was infused before drug administration. The patients received 5-fluorouracil 750 mg/m², epirubicin 30 mg/m² and mitomycin 7 mg/m² by bolus infusion. Results: All patients were evaluated for toxicity and response. Twenty-two cycles were administered. The toxicity was mild and did not influence the patients' quality of life; the compliance was excellent. A response rate of 80% (8 out of 10) was obtained; the median overall survival was 33.5 months; no patient had local recurrence. Conclusion: Intra-arterial chemotherapy is an effective and safe treatment for locally advanced breast cancer in the elderly.*

Locally advanced breast cancer (LABC) accounts for 5 to 15% of new breast cancer cases in the USA and for 40 to 60% of new cases in non-industrialized countries (1). Elderly patients are more likely to present with LABC than younger ones, furthermore, due to the increase in the aged population, the incidence of breast cancer is expected to rise in coming decades. There are no widely accepted guidelines for treatment of the elderly and appropriate clinical trials

should be designed (2). The quality of life and quality of cure are always very important, particularly in the elderly where it is mandatory to define as fit or frail each patient before treatment (3). Medical, psychological and social aspects should be carefully considered in order to plan the treatment. Absolute disease free survival benefit has been obtained in elderly patients treated with chemotherapy and hormonal therapy; MD Anderson data suggest that anthracycline-based schedules have a good tolerance profile, but cardiotoxicity must always be considered as in younger patients (4). There are not many studies of neoadjuvant chemotherapy in elderly patients with LABC, but response rate, disease free survival and overall survival have been reported as similar in elderly and younger patients (5). Major toxicity, such as myelosuppression and febrile neutropenia, has been presented as the most dangerous side-effect of chemotherapy in patients over 70 years of age (6). One possible method to decrease these systemic side-effects is intra-arterial administration (7, 8). In neoadjuvant treatment, anthracyclines have been very efficient in downstaging, alone or with other drugs (9). Many studies have reported that adriamycin concentration in cancer tissues was higher after intra-arterial infusion than after intravenous infusion: repeated higher doses of intra-arterially administered adriamycin for a short time have been reported to be more effective than lower doses over a longer period (10). Our study was designed to evaluate feasibility, toxicity and local response rate of an intra-arterial chemotherapy (IAC) regimen including 5-fluorouracil, epirubicin and mitomycin in elderly patients.

Patients and Methods

Enrolment. Patients were classified according to the 1997 American Joint Committee on Cancer criteria of breast cancer staging (11). Stage IIIB patients had tumors of any size (T0 to T3) with

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Table I. Patient characteristics.

N	Age (Years)	Stage	Grading	Size (cm)	HR	c-erbB2	Ki67 (%)
1	83	IIIB	3	5	NEG	---	30
2	78	IV liver	3	8	POS	+-	20
3	77	IIIB	3	9	NEG	++-	NE
4	75	IIIB	3	12	NEG	+++	40
5	82	IIIB	3	10	POS	---	20
6	95	IIIB	3	15	POS	---	20
7	80	IIIB	2	10	POS	---	30
8	85	IIIB	2	12	POS	+++	30
9	79	IIIB	3	8	NEG	---	30
10	82	IIIB	3	10	NEG	---	40

HR: hormonal receptor, NE: not evaluated.

metastasis to ipsilateral internal mammary lymph nodes or had tumors with direct extension to the chest wall or skin (T4) and metastasis to lymph nodes (N1-N3). Inflammatory breast cancer is defined as breast carcinoma characterized by diffuse brawny induration of the skin with an erysipeloid edge, usually without an underlying palpable mass, and it is classified as T4d (12). An incisional biopsy was carried out and pathological diagnosis of carcinoma was confirmed. In addition, estrogen and progesterone receptors were determined by immunohistochemical staining, growth fractions by monoclonal antibody Ki67 and c-erbB2 protein expression by erb-B2 monoclonal antibody. All patients gave informed consent and the study was approved by the internal ethical committee.

Treatment. All patients were treated in the angio-suite under aseptic conditions. After the administration of local anesthesia, according to the standard Seldinger technique, a 6F 11 cm long sheath was inserted percutaneously into the femoral artery and, subsequently, an arteriogram of the subclavian, internal mammary and lateral thoracic arteries was obtained for all patients. The internal mammary artery (IMA) was catheterized by the use of a 5F IMA catheter (H1 Cordis, Johnson & Johnson Medical Spa, Milan, Italy) together with a hydrophilic guidewire (RLPC-35-180).

For tumors of the outer quadrants the lateral thoracic artery was usually used for IAC. In order to confirm that the vessels supplied the tumor area, before drug administration, 5 ml of patent blue dye solution with xylocaine was injected through the catheter into the internal mammary or lateral thoracic artery. Patients received 5-fluorouracil 750 mg/m² in 50 cc of normal saline, epirubicin 30 mg/m² in 50 cc of normal saline and mitomycin 7 mg/m² in 50 cc of normal saline by bolus infusion. The treatment was repeated every three weeks. Antiemetic treatment consisted of a 5HT₃ antagonist agent (ondasetron) plus dexamethasone administered by systemic infusion for 15 minutes before starting chemotherapy.

Response criteria. Following the WHO criteria the response was estimated according to the clinical features after the treatment: complete disappearance of all the lesions was considered a complete response (CR), macroscopic reduction in size by at least 50% was considered a partial response (PR); a reduction of between 25% and 50% was designated stable disease (SD); the

appearance of any new lesions not previously identified or an estimated increase of 25% in existent lesions was considered progressive disease (PD).

Results

Patients. Ten patients were enrolled in this study. Patient characteristics are listed in Table I. Nine out of ten patients were classified as UICC stage IIIB: all were fungating through overlying skin and five presented fixed involved axillary lymph nodes. One patient was classified as stage IV because of the involvement of the liver, with a primary tumor mass of 12 cm with severe local bleeding; two had inflammatory breast cancer. All patients were females, the median age was 82 years (range 75-95) and the tumor size ranged from 5 to 15 cm, with an average of 10 cm. Eight patients had a poorly-differentiated tumor and two patients had a moderately-differentiated tumor. Hormonal receptors were positive in five patients; two patients were c-erbB2 positive (+++) and Ki67 values were 20% in three patients, 30% in four and 40% in two. In nine out of the ten patients the drugs were infused into the mammary artery, in one patient treatment was also performed in the lateral thoracic artery, because the internal mammary artery did not adequately perfuse the breast. All patients were evaluable for toxicity and response.

Toxicity. Twenty-two cycles were administered with a median of 2.2 (range 1-3). No side-effect related to angiographic technique was observed. Systemic side-effects were minimal and did not influence the patients' quality of life.

Two patients had grade 1 hematological toxicity without fever or bleeding related to leucopenia or thrombocytopenia. Two patients presented grade 1 nausea; no patient had vomiting, gastric pain, diarrhoea or mucositis. In two patients transient cerebrovascular ischemia was observed,

Table II. Results of intra-arterial chemotherapy with 5-fluorouracil, epirubicin and mitomycin.

N	Cycles	Response	Surgery	Time to Surgery (days)	Survival (months)	Status
1	2	PR	Yes	34	11.0	Alive
2	3	SD	No	-	20.3	Dead
3	2	PR	Yes	34	7.1	Dead
4	3	SD	No	-	15.3	Dead
5	3	PR	Yes	62	127.0	Alive
6	2	PR	No	-	17.2	Dead
7	2	PR	Yes	72	33.5	Dead
8	2	PR	Yes	57	28.4	Alive
9	2	PR	Yes	39	26.3	Alive
10	1	PR	No	-	28.3	Alive

PR: partial response, SD: stable disease.

probably related to a reversible spasm of internal carotid. Cardiovascular toxicity was not observed. Two patients presented grade 2 alopecia. Local toxicity consisted in one case of erythema of the skin, probably due to drug streaming, which was cured without skin damage.

Response. The results are summarized in Table II. Eight PR were observed, with an overall response rate of 80%; the other two patients presented SD. In responder patients, a tumor reduction after the first cycle was observed. Following this loco-regional treatment six patients went on to radical surgery. The mean interval between the first cycle and mastectomy was 41 days (range 34-72). Among the other four patients, one was not submitted to mastectomy because of age (95 years) and the other three did not reach operability, two had SD and the third presented transient cerebrovascular ischemia after the first cycle of loco-regional chemotherapy. After IAC, patients with positive hormonal receptors received tamoxifen or aromatase inhibitors; one patient received systemic therapy and no one was submitted to radiotherapy. The median dose of epirubicin administered was 66 mg/m² (range 30-90). After a median follow-up of 23 months (range 7-127), five patients had died; one from progressive disease at 7.1 months and the others from other causes not cancer related. The median overall survival was 33.5 months, with a 1-, 2- and 5-year survival of 85%, 56% and 28%, respectively.

Discussion

Our study showed that IAC in elderly patients with LABC is feasible and effective. A high local response rate (80%) was achieved in short time, with optimal compliance of the patients due to the very low incidence of systemic toxicity. It is known that in patients with LABC the primary aim of treatment is to gain long-term local control, although it is also important to treat micrometastasis. Loco-regional

chemotherapy could have a two-fold benefit: local control and prevention of systemic metastases (13). Local control was obtained in a short time: in most patients breast masses were already softened after the first cycle; metastatic axillary nodes generally decreased more than the primary lesions, probably because epirubicin was distributed at higher concentrations in the lymphonodes than in the primary lesions (7). The role of primary systemic chemotherapy in LABC had been established by a number of clinical trials performed in the 1990's (9, 14). Recently some phase II studies are published about primary chemotherapy in LABC (15, 16). However the extrapolation of these data to elderly patients (>75-years-old) is not always straightforward. These patients have been historically excluded from clinical trials; their management has been generally individualized frequently posing a dilemma, even though the trend now is to treat them. A multidisciplinary team including also social and nursing support is essential for the optimal management of elderly patients (3). The practice of oncology should be related to the special characteristics of the older population which include a high degree of diversity in life expectancy, treatment tolerance and social resources. It has not been established whether the front-line chemotherapy is better when given by intra-arterial or intravenous infusion; however, some small clinical trials have clearly confirmed the high response rate, the low systemic toxicity and the good patients compliance with this loco-regional approach (17, 18).

In conclusion, we would like to emphasize the efficacy of this loco-regional treatment for the elderly; only one day of hospitalization is necessary for each course of chemotherapy and its tolerability is excellent. In everyday practice, it is common to treat patients over 80-years-old only with hormonal therapy; the feasibility and tolerability of IAC, which was clearly demonstrated in our study, might highlight some advantages for this probably under-treated group of patients.

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