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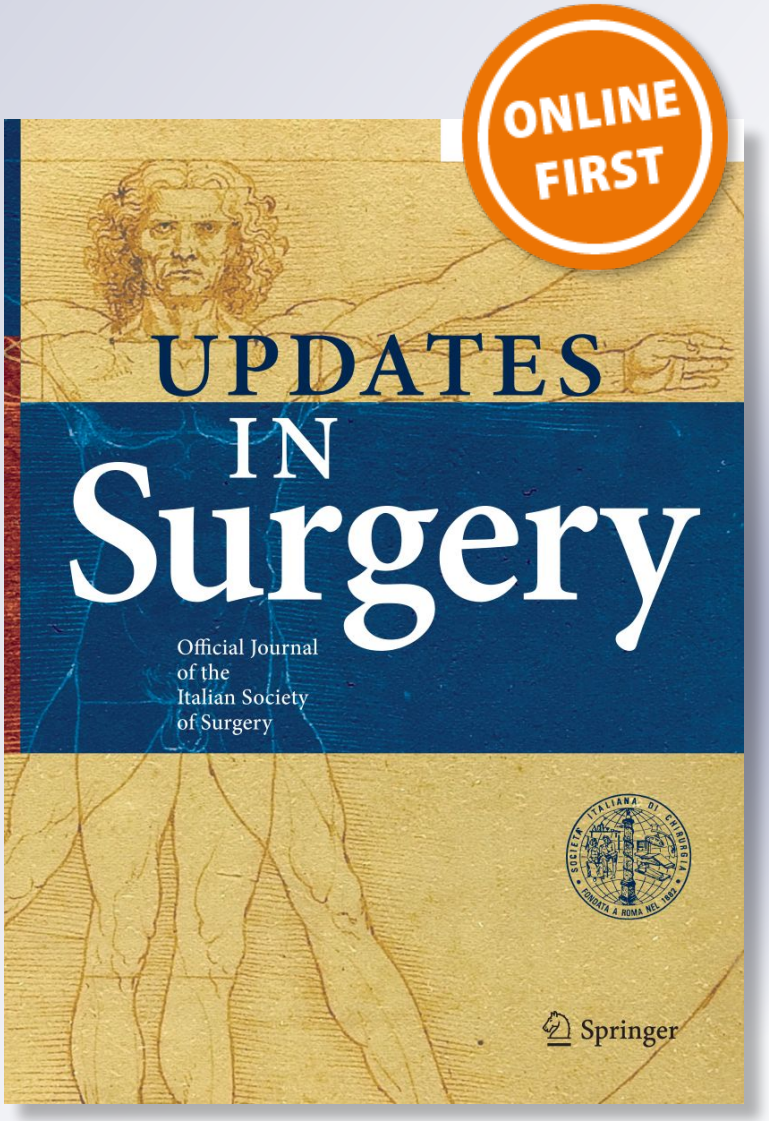

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ORIGINAL ARTICLE

Isolated thoracic perfusion in lung metastases from breast cancer: a retrospective observational study

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Abstract

The median overall survival of metastatic breast cancer (MBC) patients is still approximately 2 years. This is even lower in triple-negative breast cancer (TNBC) patients with concomitant lung metastases. These patients are often not suitable for surgery and not responsive to systemic chemotherapy. Isolated thoracic perfusion (ITP) followed by chemofiltration has been used for palliation in selected specialised centres. A retrospective observational study evaluating 162 MBC patients who underwent 407 ITP procedures was performed. The primary objective was the evaluation of the feasibility, safety, tolerability and efficacy of ITP in the complete cohort of 162 patients with LM from breast cancer. The secondary objective of the study was the evaluation of responses and median survivals in 43 TNBC patients with LM. In the 162 patients, ITP appeared safe and well tolerated with MST from LM diagnosis to death or last contact of 19.5 months. In the subgroup of patients treated with systemic chemotherapy followed by ITP at progression, the MST from LM diagnosis to death or last contact was 29 months. In the subgroup of TNBC patients treated with systemic chemotherapy followed by ITP at progression, the MST from LM diagnosis to death or last contact was 19 months (ITP overall response rate was 65.52%). ITP followed by chemofiltration could be adopted in the sequential palliation treatments of BC patients with LM in progression after systemic chemotherapy, especially with TNBC. The present data allow interesting considerations about tolerability and responses, but do not allow robust conclusions about survival.

Keywords Breast cancer · Lung metastases · Triple-negative status · Isolated thoracic perfusion

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Introduction

Advanced breast cancer (ABC) is defined as malignant breast neoplasm that comprises both inoperable locally advanced and metastatic breast cancer. Despite the improving efficacy of different chemotherapeutics associations, and the approval of targeted and biological agents in different settings of breast cancer patients, ABC remains a disease with a median overall survival of approximately 2 years [1].

Metastatic breast cancer (MBC) requires a multidisciplinary management to extend overall survival and preserve or improve quality of life [2]. Both combination and sequential single-agent chemotherapy may be appropriate as first-line systemic therapy, according to the clinical situation [3]. For MBC patients with progressive disease after systemic first-line chemotherapy, especially triple-negative breast cancer (TNBC) patients, there are different treatment options recommended, not all with significant level of evidence. However, sequential palliative systemic chemotherapy until progression may compromise quality of life, even if it offers better disease control and overall survival improvement [4]. For this reason, also other types of palliative therapy are considered as option for disease control [2].

It has been reported that the incidence of lung metastasis can reach up to 40% in TNBC patients [5]. These patients are often not suitable for surgery and non-responsive to systemic chemotherapy; they can also be affected by the so-called multiple chronic conditions (e.g. impaired heart, renal or liver function, or autoimmune disease). Overall survival of this subset of patients has not improved in the last 20 years, even if several registered trials are ongoing [6]. Isolated thoracic perfusion (ITP) has been adopted in a few specialist centres as treatment option for them [7], but its efficacy has not been evaluated in a large cohort of patients. Safety and efficacy of ITP have been reported in phase I–II studies for advanced pleural mesotheliomas [8, 9], advanced lung cancer [10], and advanced thoracic lymphomas [11]. Chemofiltration has been used at the end of ITP to reduce drug-related side effects [7], resulting in a safe and effective procedure [12]. Major limitation of ITP is its complexity making it not feasible in medical oncology units and rarely performed in not specialist surgical centres.

In this retrospective observational study, we evaluated the safety profile of ITP in breast cancer patients with lung metastases, then focusing our attention on the subgroup of TNBC patients.

Materials and methods

Patient eligibility

This retrospective observational study included 162 patients who had undergone a total of 407 ITP procedures followed by chemofiltration in the period 1990–2016 in multiple centres (Department of Surgical Oncology, Medias Klinikum, Burghausen, Germany; Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy; Department of Surgical Oncology, University of Crete, Heraklion, Greece). Inclusion criteria were: (1) histologically confirmed diagnosis of breast cancer; (2) lung metastases (LM), measurable, judged unrespectable by thoracic surgeons and refractory to systemic therapy; (3) age 18–85 years; (4) World Health Organization performance status (PS) ≤ 2; (5) adequate haematological, renal, hepatic functions; (6) life expectancy > 3 months.

Exclusion criteria were: (1) ventricular ejection fraction EF $< 50\%$; (2) neutropenia with blood cells $< 1000/mm^3$; (3) deep venous thrombosis; (4) severe atherosclerosis; (5) severe coagulopathies; 6) ECOG performance status 3–4 or Karnofski index $< 50\%$.

Patients had provided written informed consent after complete information about the disease and implications of the proposed palliative treatment. This retrospective observational study had been conducted in accordance with the ethical standards of the Committee on Human Experimentation, after approval of the Ethics Committee in L'Aquila (n.10/CE/2018), and according to all rules for good clinical practice included in the Declaration of Helsinki.

For the purposes of this publication, from the database of 162 patients, a subset of 43 TNBC patients was subsequently selected and information on their overall survival reported.

Treatment schedule

Patients were perfused with mitomycin C (MMC) at doses of 25 mg/m^2 and cisplatin at doses of 80 mg/m^2. Doses were established according to previously published studies [8–10]. Enrolled patients underwent a maximum of four ITP treatments associated with chemofiltration, every 8 weeks. ITP was not repeated if the patient did not consent, metastases progressed more than 20% in dimension, simultaneous distant relapses occurred, general conditions worsened and in case of complete response.

Perfusion procedure

A thoracic perfusion consists in the limitation of the greater circulation to the target region such as the thorax, including

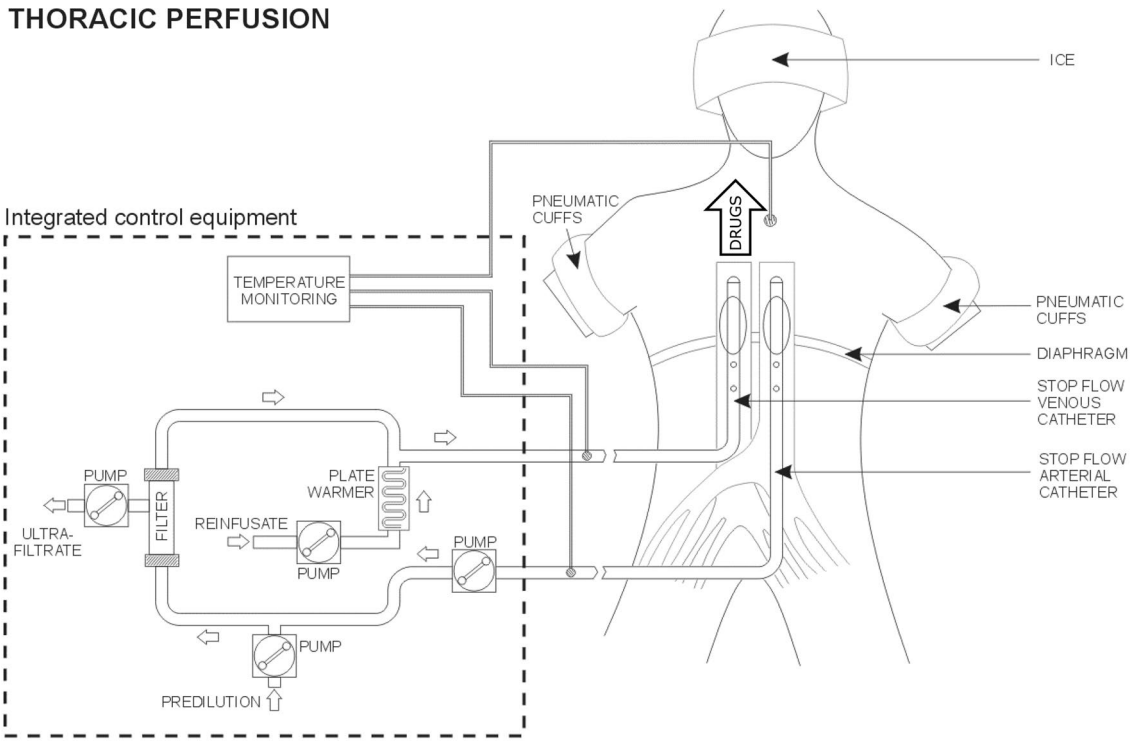

Fig. 1 Scheme of isolated thoracic perfusion with chemofiltration

the head, for a period of approximately 25 min (Fig. 1). After systemic heparinisation (150 U/kg heparin), a 3-lumen, 12-Fr. balloon catheter (pfm medical AG, Cologne, Germany) was surgically introduced into the inferior vena cava via the saphenous vein and into the thoracic aorta via the femoral artery; the catheters were positioned at diaphragm level using a guide wire under fluoroscopic guidance. After the second or third ITP, further procedures were performed by iliac vessels, exposed via an abdominal extra-peritoneal approach. One of the three lumens of each catheter was used for inflating the balloons and the other lumens for positioning the guide wire and for blood circulation during the chemofiltration phase. To avoid greater volume displacements, both balloons were inflated simultaneously. To complete isolation, two pneumatic cuffs were inflated at both roots of the arms (250 mmHg). Thoracic perfusion was regulated by the heart pump. During ITP, continuous monitoring of the thoracic aorta blood pressure was registered using an extensible wire linked to the guidewire lumen of the aortic catheter and connected by an arterial line transductor to a computer monitor. Cytotoxic drugs were delivered as bolus injection within the first 3 min of the perfusion using the guidewire line of venous catheter. After deflating the balloons, catheters were used to activate an extracorporeal blood circulation with the purpose of performing a chemofiltration to reduce systemic toxic effects. Chemofiltration was controlled by a circulation device (Performer LRT; RanD, Medolla, Italy) containing a heating element and a chemofiltration module. The blood was withdrawn from the aorta with a flow of approximately 200 mL/min. The temperature at the outlet level of the heating element was 39 °C. A polyamide haemofilter with a surface area of 2.1 m^2 (RanD, Medolla, Italy) was used for filtration. The duration of chemofiltration was approximately 50 min. At the end of the procedure, the catheters were pulled out and the vessels repaired. Protamine was injected at 200 IU/kg to reverse the anticoagulant effects of heparin.

Anaesthesia and haemodynamics

All 407 ITP were performed under general anaesthesia, as previously described [13]. ITP did not require a routine pulmonary artery catheterisation, except in high cardiac risk patients. Central venous catheterisation, however, should be regarded as the minimum level of monitoring for such procedures. During ITP, a temporary increase of approximately 25% of the mean arterial pressure and a mean value of 120 mmHg in the thoracic district have been previously reported [13].

Adverse events and response

Adverse events were assessed using National Cancer Institute Common Toxicity Criteria (CTCAE v4.03). Tumour

response was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) [14]; responses of patients treated before 2009 were retrospectively re-classified. Clinical evaluation of response was made by computerised tomography scan; positron emission tomography was added based on investigators' assessment; objective responses were confirmed 3 months later. Follow-up was scheduled every 3 months up to disease progression or death.

MMC pharmacokinetic study

Thoracic and systemic blood samples were obtained to monitor MMC. Peripheral blood samples were collected in 4-ml heparin tubes at the following time points: 0, 5, 10, 15, 20, 25, 30, 45, 60 and 80 min, while thoracic compartment blood samples were collected at 0, 5, 10, 15, 20 and 25 min from the superior vena cava. The 0-min time point is defined as being immediately before the drug was injected into the thoracic compartment. After all samples were collected, they were centrifuged at 3000*g* at 4 °C for 10 min. The plasma was removed and aliquoted in 1 ml amounts into tubes and stored at − 20 °C until high-performance liquid chromatography (HPLC) analysis of the MMC concentrations was performed [15]. For the pharmacokinetic analysis, a non-compartmental model for plasma MMC concentrations was chosen and applied using a computer program [16]. For chemofiltration from 25 to 80 min, the total MMC removal (TMMCR) was calculated from the ratio between MMC concentrations in the ultrafiltrate and MMC concentrations in the blood coming out of the aorta of the patient.

End points and statistical analysis

The primary objective was the evaluation of feasibility, safety, tolerability and efficacy of ITP in the complete cohort of 162 patients with LM from breast cancer. Details about the following aspects have been registered: (1) procedure-related complications; (2) ITP-related toxicity; (3) pharmacokinetic study; (4) responses; (5) survivals.

The secondary objective of the study was the evaluation of responses and median survivals in the 43 patients with LM from TNBC treated with ITP and chemofiltration.

The analysis provided descriptive statistics estimated with 95% confidence intervals. Survival was estimated using the Kaplan–Meier product limit estimator. Overall survival (OS) was defined as length of time between beginning of treatment and death or last contact. We recorded deaths due to progression of cancer. Deaths due to other causes and patients still alive at the end of the observation period were censored.

Survival times were stratified according to the clinical variables that potentially affect survival. A table of at-risk patients was prepared for each variable when comparing survival times, and log-rank tests were used to assess the significance of the differences between the groups. Hazard ratios were estimated by using a proportional hazard Cox regression model. The assumption of proportional hazards was tested by using the Schoenfeld test. The statistical analysis was performed using STATA software, version 14 (StataCorp, College Station, Texas). Means ± standard deviations were presented.

Results

Patients' features and treatments

One-hundred and sixty-two patients with LM from breast cancer were enrolled; their mean age was 51.97 ± 11.92 SD (median 52, IQR 44–60). Each patient underwent a median number of 3 ITP, and 407 procedures were performed and included in the analysis. Table 1 reports patients and tumour characteristics. Forty-three patients had triple-negative profile. Seventy-eight LM patients included did not receive previous systemic chemotherapy because of refused or withdrawn consent due to fear of chemotherapy side effects or for other reasons such as distance to the hospitals, shortage of transport, personal or religious beliefs (Fig. 2). In 85 patients, ITPs were performed before 2000, in 33 patients before 2010, and in 44 patients before 2017. Two patients were lost to follow-up in this study and no patients died of other causes. Median follow-up from BC diagnosis was 51 months [IQR 31–99]. Median follow-up from LM diagnosis in BC patients to death was 19.5 months [IQR 12–34].

With regard to the 43 TNBC patients, 29 LM patients were in progression after systemic chemotherapy (anthracycline-based chemotherapy regimen in 9 patients, anthracycline and taxane therapy in 17 patients, unknown in 3 patients). In 19 patients, ITPs were performed before 2000, in 12 patients before 2010, and in 12 patients before 2017. None of the 43 patients received any kind of antitumoural therapy after the last ITP.

Primary endpoints: feasibility, safety, tolerability and efficacy of ITP in the complete cohort of patients with lung metastases from breast cancer

Procedure-related complications

There were no haemodynamic or vascular complications during the 407 perfusions, and no perfusion-related postoperative deaths. One technical complication (balloon catheter rupture) was registered. Femoral or iliac cannulation was always possible. The complications registered in patients undergoing the procedure have been reported in Table 2.

Table 1 Patient, tumour, and treatment characteristics

Patient, tumour, and treatment characteristics	*N*	%
Patients with lung metastases from breast cancer	162	100
Gender		
Female	160	98.77
Male	2	1.23
Age		
≤40 years	34	20.99
>40 years	128	79.01
Origin		
Northern Europe (Germany)	114	70.37
Southern Europe (Italy, Greece)	21	12.97
Other (East Europe or Asia)	27	16.67
Histology		
Ductal	156	96.30
Lobular	3	1.85
Other	3	1.85
Metastatic sites		
Lung limited	114	70.37
Lung and other sites	48	29.63
Previous systemic chemotherapy		
Yes	84	51.85
Not	78	48.15
Triple-negative profile		
Yes	43	26.54
Not	119	73.46
Malignant pleural effusion		
Yes	9	5.56
Not	153	94.44
Mastectomy and homolateral lymphoadenectomy		
Yes	161	99.38
Not	1	0.62
Multiple chronic conditions		
Yes	2	1.23
Not	160	98.77
Number of ITP		
1	35	21.60
≥2	127	78.40
Any therapy after ITP		
Yes	9	5.56
Not	153	94.44

ITP with chemofiltration-related toxicity

No severe perfusion-related haematologic toxicity was reported (Table 2). Grade 2 and grade 3 haematologic toxicity was registered in less than 2% of patients. Granulocyte colony-stimulating factor was administered in patients with G3 neutropaenia. Other toxicities were: G2 alopecia in 30 patients (18.5%) and G1–2 nausea and vomiting in 25 patients (15.4%). G1 Platinum-induced neurotoxicity was registered in 16 patients (9.9%). G2 dyspnoea and fatigue were registered in 38 patients (23.4%).

MMC pharmacokinetic study

Time-counting curves showed a continuous leakage from thoracic to systemic compartments evaluated in 17 patients (Fig. 3a). The MMC pharmacokinetic parameters, such as maximum plasma concentration (C_{max}) and area under the plasma concentration curve ($AUC_{0–25}$), were in favour of a greater thoracic exposure than that of the systemic compartment (Table 3Part A). The mean thoracic/systemic $AUC_{0–25}$ ratio was 4.24. Table 3Part A also reports mean values ± SD for the thoracic C_{max} and for the ratio of the MMC C_{max} values in the thoracic and systemic compartments.

For chemofiltration, time-counting curves showed a constant MMC clearance from the systemic compartment between 25 and 80 min (Fig. 3b). The average TMMCR in the blood during the chemofiltration phase (25–80 min) was approximately 28%. Table 3Part B also reports other pharmacokinetic parameters in the peripheral blood that were calculated during the entire procedure time (0–80 min).

Responses

For the activity of ITP, Fig. 4a reports the percentage of responses in all 407 procedures; a comparison of the response rates of the 43 TNBC patients with LM has been also shown. A total of 48.8% (complete and partial) responses were registered in the 162 BC patients with LM. A total of 51.2% responses were measured in the 43 TNBC patients with LM; unfortunately, the percentage of progressions in TNBC patients was also higher than that of the entire cohort (32.56 versus 20.99%).

Median survival times of the entire cohort of BC patients with LM who underwent ITP

The median interval time in the 162 patients from the BC diagnosis to the LM diagnosis was 28.5 months. The MST of these patients from LM diagnosis to death or last contact was 19.5 months. The MST from initial ITP to death or last contact was 14 months. In the subgroup of patients treated with systemic chemotherapy followed by ITP at progression, the MST from LM diagnosis to death or last contact was 29 months.

The 1-year, 3-year, and 5-year survival rate after ITP from LM diagnosis was 74.69, 29.63, and 24.07%, respectively. Number of metastatic sites and previous systemic chemotherapy significantly affected the MST after ITP (Fig. 4b); age, histology, multiple chronic conditions, and geographical origin did not. Thirty-five BC patients with LM underwent only 1 ITP; further ITP was not carried out

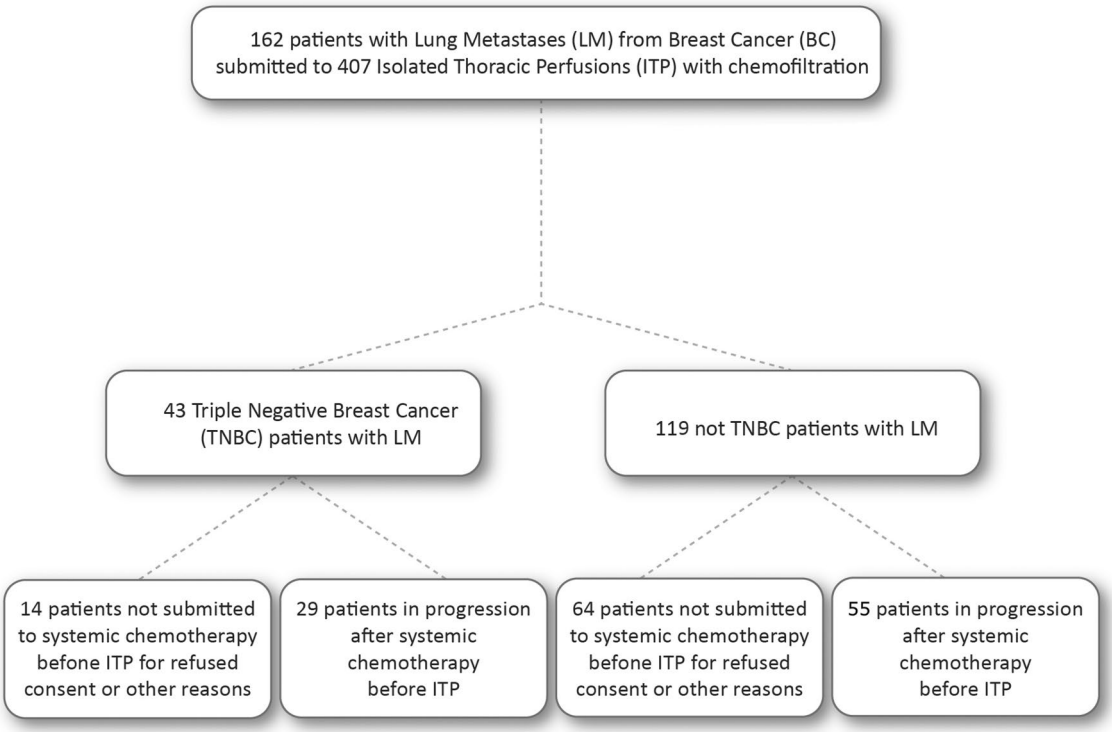

Fig. 2 Study design

Table 2 Procedure related complications and toxicity after 407 ITPs in 162 BC patients with LM

	BC patients with LM ($n=162$)	TNBC patients with LM ($n=43$)
	Number of patients (%)	Number of patients (%)
Complications		
Femoral vein thrombosis	2 (1.23)	–
Seroma	17 (10.5)	1 (2.3)
Persistent leakage of fluid from the incision	23 (14.2)	3 (6.9)
Wound infection	8 (4.9)	1 (2.3)
Inguinal haematoma	4 (2.5)	–
Wound dehiscence	7 (4.3)	2 (4.6)
Lymphangitis	4 (2.5)	1 (2.3)
Toxicity		
Bone marrow hypocellularity		
Grade 1	24 (14.8)	7 (16.3)
Grade 2	7 (4.3)	2 (4.6)
Grade 3	3 (1.8)	–
Alopecia	30 (18.5)	7 (16.3)
Nausea and vomiting	25 (15.4)	5 (11.6)
Platinum-induced neurotoxicity	16 (9.9)	4 (9.3)
Dyspnoea and fatigue	38 (23.4)	11 (25.6)

due to refused consent in 17 cases (48.57%), progression in 3 cases (8.57%), worsening of general conditions in 12 cases (34.28%), and complete response in 3 cases (8.57%), respectively. Malignant pleural effusion, although registered in a small number of nine patients (Table 4Part A), resulted in a high-risk prognostic factor (HR 3.45, $p=0.0001$).

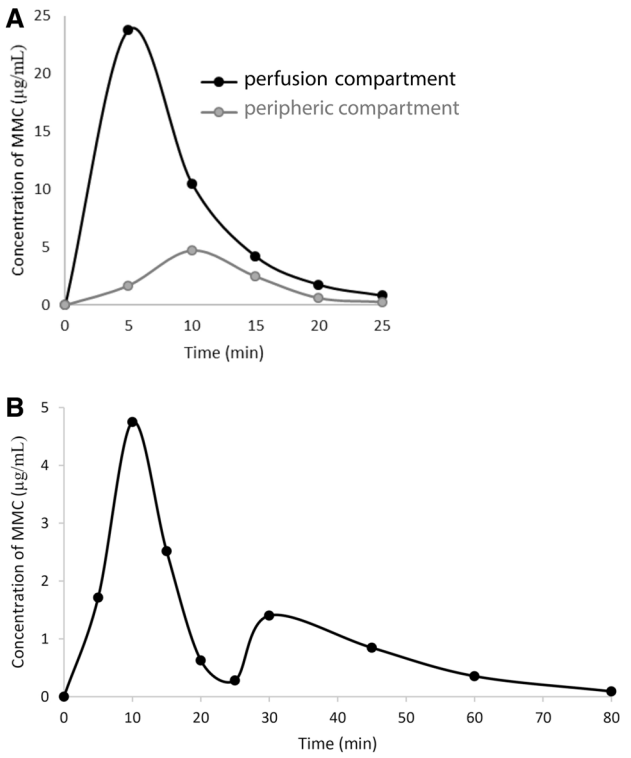

Fig. 3 **a** MMC pharmacokinetic time-counting curves (0–25 min) determined for 17 patients in the blood of isolated thoracic perfused compartment and in the venous blood of the peripheral compartment. Black curve—isolated thoracic perfused compartment. Grey curve—peripheral compartment. **b** The chemofiltration efficacy has been demonstrated by the MMC clearance time-counting curve (0–80 min) determined for 17 patients in the peripheral venous blood. The first peak corresponds to the isolated perfusion phase; the second peak was registered when the catheter balloons were deflated

Prolonged values of survival times from LM diagnosis to death or end of follow-up were statistically associated (Log-Rank $\chi^2 = 27.08$, $p < 0.0000$) with the interval times between BC diagnosis and LM diagnosis, fixing the most statistically significant cutoff point at 34 months.

Secondary end points: responses and median survival times of TNBC patients with LM

The median interval time of 43 TNBC patients from the BC diagnosis to the LM diagnosis was 23 months. The MST of these patients from LM diagnosis to death or last contact was 10 months. In the subgroup of patients treated with systemic chemotherapy followed by ITP at progression, the MST from LM diagnosis to death or last contact was 19 months. The response percentages after ITP are reported in Fig. 4a. Overall response rate in the subgroup of 29 TNBC patients with LM in progression after systemic chemotherapy and undergoing ITP was 65.52% (CR = 3.45%, PR = 62.07%). The 1-year, 3-year, and 5-year survival rate after ITP from LM diagnosis

Table 3 Part A: MMC pharmacokinetic parameters measured in the thoracic blood of 17 patients during isolated thoracic perfusion (0–25 min), Part B: MMC pharmacokinetic parameters measured in the peripheral blood of 17 patients during the isolated thoracic perfusion and chemofiltration phases (0–80 min)

	Mean ± SD	Range
Part A (isolation phase)		
AUC_{0-25} perfused compartment/ AUC_{0-25} peripheral compartment	4.24 ± 0.73	3.19/5.78
C_{max} perfused compartment (µg/mL)	23.77 ± 2.49	19.45/27.80
C_{max} perfused compartment/C_{max} peripheral compartment	5.23 ± 1.15	3.49/8.86
Part B (peripheral blood)		
C_{max} (µg/mL)	4.78 ± 0.95	2.94/6.01
AUC_{0-0} (µg/mL*min)	83.27 ± 13.53	62.20/100.32
$t_{1/2}$ (min)	11.25 ± 3.15	6.66/16.73
V_d [mg/(µg/mL)]	4.83 ± 1.24	2.61/6.75
CL [mg/(µg/mL)/min]	0.30 ± 0.05	0.22/0.39
$TMMCR_{25-80}$ (%)	28.19 ± 5.08	24.27/33.52

AUC_{0-25} area under the plasma concentration curve (0–25 min), estimated by the linear trapezoidal method, C_{max} maximum plasma concentration, AUC_{0-80} area under the plasma concentration curve (0–80 min), $t_{1/2}$ half-life of elimination phase, V_d volume of distribution, *Cl* total clearance (extracorporeal plus systemic), *TMMC* total MMC removal

was 67.44, 13.95, and 6.98%, respectively. Malignant pleural effusion, number of metastatic sites, and previous systemic chemotherapy significantly affected survival (Fig. 5b), whereas age, histology, multiple chronic conditions, and geographical origin did not (Table 4Part B). Thirteen TNBC patients with LM underwent only 1 ITP; further ITP were not carried out because of refused consent in 6 cases (46.15%), progression in 2 cases (15.38%), and worsening of general conditions in 5 cases (38.46%), respectively.

In 29 TNBC patients, ITP provided 11 months of MST when performed after systemic chemotherapy, with MST from LM diagnosis of 19 months (Fig. 5a). ITP provided 7 months of MST when performed without any previous systemic chemotherapy, with MST from LM diagnosis of 8 months (Fig. 5a). The hazard risk was 2.60 times higher for patients with more than one site of metastasis and malignant pleural effusion compared to that of patients with lung-limited metastases without malignant pleural effusion (Table 4Part B).

Discussion

This study demonstrates that ITP for BC patients with LM is feasible, safe and tolerable, with approximately 50% of response rate and a median overall survival of 29 months

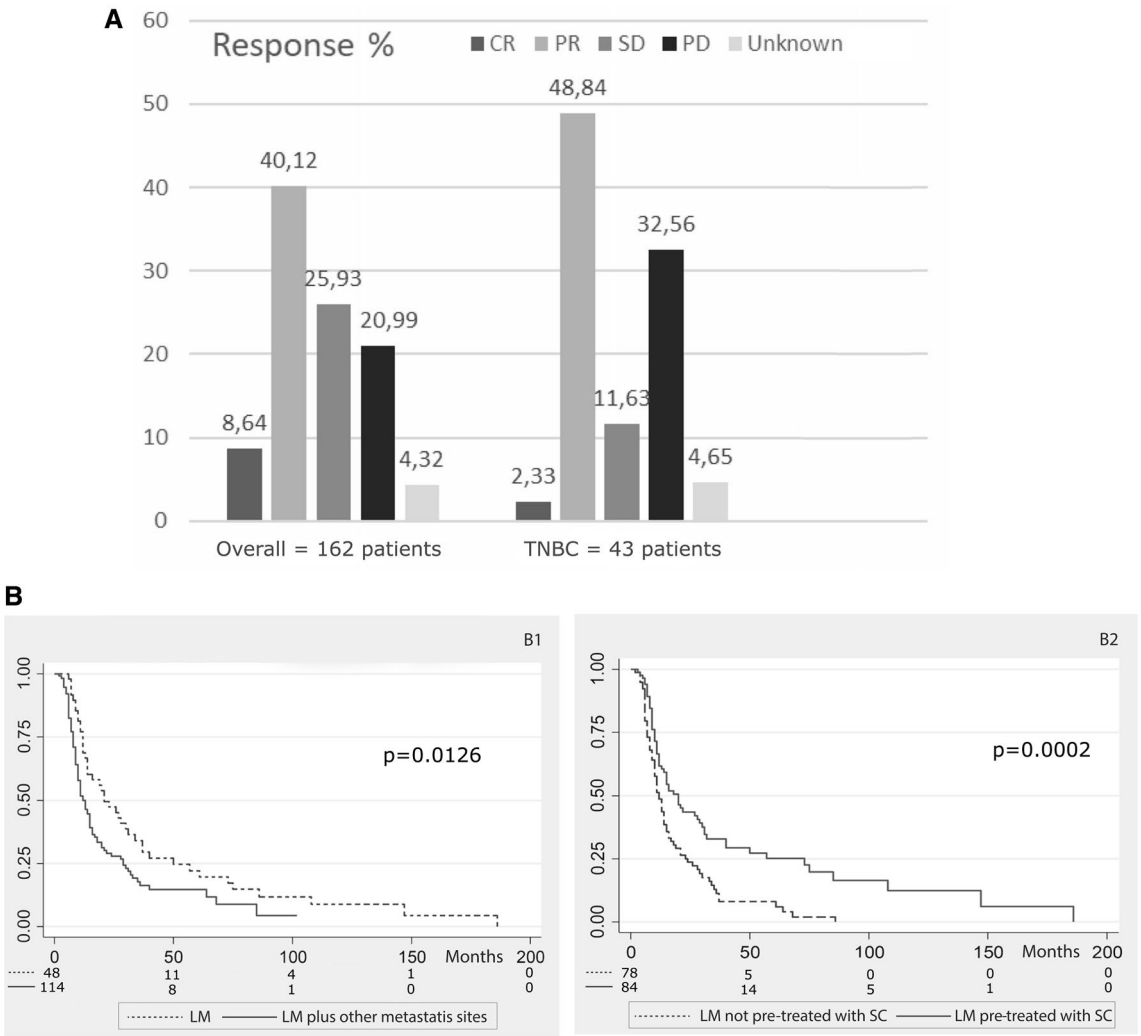

Fig. 4 **a** Percentages of complete responses (CR), partial responses (PR), stable disease (SD), progressive disease (PD), unknown response (Unknown) in the overall series (162 cases), and in the TNBC patients with LM (43 cases). **b** Kaplan–Meier survival curves in 162 breast cancer patients with LM treated by ITP. *B1* Lung-limited metastatic site versus LM with other metastatic sites. *B2* LM pre-treated with systemic chemotherapy versus LM not pre-treated with systemic chemotherapy

from the diagnosis of LM when the patients were pre-treated and in progression after systemic chemotherapy. Indication of ITP for LM in the presence of other concomitant relapses is based on palliation of pulmonary symptoms, the progression of which is harrowing and negatively influences the perceived quality of life of the patients [1, 2]. This study also showed that ITP may provide a 51% response rate in TNBC patients in progression after systemic chemotherapy; the median overall survival from the diagnosis of LM in this subgroup of patients was 19 months. The median survival from the initial ITP was significantly lower in case of concomitant malignant pleural effusion (6.5 months) or in the presence of other metastatic sites (7 months).

With regard to the comparison with a treatment based on systemic chemotherapy only for TNBC patients with LM, a combination or single systemic chemotherapy regimens did not provide better results [6, 17]. In a retrospective study [17], TNBC patients with lung metastases had the longest median post-metastatic overall survival of 16.6 months, followed by the bone (16.3 months), the liver (8.9 months), the pleura (7.5 months), and the brain, (4.3 months). A median survival of 18 months has been reported for TNBC patients with LM in a retrospective observational study based on systemic chemotherapy [18]. Microtubule inhibitors (taxanes) provided approximately 12–15 months of MST in patients with MBC (25% TNBC) who previously progressed after an anthracycline-based chemotherapy regimen [19]. Eribulin provided approximately 11–16 months of MST in MBC patients (approximately 25% TNBC) who had received prior anthracycline and taxane therapy [20, 21]. A phase II study in MBC patients reported that capecitabine with bevacizumab provided an overall survival of 7.5 months

Table 4 Median survival time (MST) from initial ITP and hazard ratios (HR) according to gender, age, geographical origin, histology, metastatic sites, previous systemic chemotherapy treatment of LM, malignant pleural effusion, and multiple chronic conditions (e.g. impaired heart, renal or liver function, or autoimmune disease)

Patient and tumour characteristics	*N*	%	MST (months)	Log rank χ^2	*p* value	Cox HR
Part A						
BC patients with LM	162	100	14			
Gender						
Female	160	98.77	14	ns	ns	ns
Male	2	1.23	ns			
Age						
≤40 years	34	20.99	12.5	ns	0.12 ns	0.73 ns
>40 years	128	79.01	14			
Origin						
Other (East Europe or Asia)	27	16.67	17	8.25	0.04	1.53 ns
Central Europe (Germany)	114	70.37	14.5			
Southern Europe (Italy, Greece)	21	12.97	9.5			
Histology						
Ductal	156	96.30	14	ns	ns	ns
Lobular	3	1.85				
Other	3	01.85				
Metastatic sites						
Lung limited	48	29.63	21	6.23	.0126	1.60 (0.02)
Lung and other sites	114	70.37	12			
Previous systemic chemotherapy						
Yes	84	51.85	16	14.13	0.0002	0.53 (0.0001)
Not	78	48.15	12			
Malignant pleural effusion						
Yes	9	5.56	7	14.81	0.0001	3.45 (0.0001)
Not	153	94.44	14			
Multiple chronic conditions						
Yes	2	1.23	15	ns	ns	ns
Not	160	98.75				
Any therapy after ITP						
Yes	9	5.56	13	ns	ns	ns
Not	153	94.44				
Part B						
TNBC patients with LM	43	100	10			
Gender						
Female	43	100	ns	ns	ns	ns
Male	0	0				
Age						
≤40 years	16	37.21	9.5	ns	0.69	0.88 ns
>40 years	27	62.69	10			
Origin						
Other (East Europe or Asia)	4	9.30	12	ns	0.36 ns	0.94 ns
Central Europe (Germany)	21	48.84	11	ns		1
Southern Europe (Italy, Greece)	18	41.86	8.5	ns		1.54 ns
Histology						
Ductal	40	93.02	9.5	ns	ns	ns
Lobular	1	2.33				
Other	2	4.65				
Metastatic sites						
Lung limited	17	39.53	12	8.58	0.0034	2.60 (0.007)
Lung and other sites	26	60.47	7			

Table 4 (continued)

Patient and tumour characteristics	*N*	%	MST (months)	Log rank χ^2	*p* value	Cox HR
Previous systemic chemotherapy						
Yes	29	67.44	11	4.35	0.0370	0.49 (0.05)
Not	14	32.56	7			
Malignant pleural effusion						
Yes	8	18.60	6.5	6.28	0.0122	2.57 (0.022)
Not	35	81.40	11			
Multiple chronic conditions						
Yes	2	4.65	7			
Not	41	95.35	10	ns	ns	ns

Data are reported for the whole series of 162 BC patients with LM who underwent ITP (Part A) and for 43 TNBC patients with LM who underwent ITP (Part B)

ns not significant

in TNBC patients [22]. A recent study, named TNT trial, reports preliminary data on the superior activity of single agent platinum chemotherapy compared with single-agent taxane in patients with TNBC- and BRCA1/2-associated breast cancer [23].

A strength of the mitomycin C and cisplatin locoregional chemotherapy regimen utilised in this study was the overall response rate (approximately, 50%) registered in TNBC patients with LM progressing after systemic chemotherapy. Platinum-based chemotherapy combinations had a higher rate of pathologic complete response than that of non-platinum regimens also in systemic administration [6]. These regimens are nowadays still adopted in several studies in relation to the high efficacy in cancers that arise in the setting of a germline mutation in the suppressor breast cancer susceptibility gene 1 (BRCA1), many of which are TNBC [6].

Gene expression profiling studies have suggested that TNBC patients with LM might be sensitive to the inhibition of epidermal growth factor receptor (EGFR), or polyadenosine diphosphate-ribose polymerase (PARP), or the protooncogene Src, or androgen receptor, and several clinical trials are currently underway but no definitive data are available [6]. There were limited data to suggest a therapeutic benefit from immune checkpoint inhibitors, vaccines, or chimeric antigen receptor T cell therapy in MBC [6].

The safety and efficacy of ITP have been reported in advanced pleural mesotheliomas [8, 9], advanced lung cancer [10], and advanced thoracic lymphomas [11]. In this series, significantly larger than the above studies, ITP has been confirmed as a feasible, safe, and tolerable procedure in LM TNBC patients, according to results in terms of procedure-related complications and toxicity, and according to the pharmacokinetic study. No serious adverse events were reported in overall patient population enrolled. G2–3 haematological toxicity and platinum-induced neurotoxicity were registered in less than 10% of patients; this was due, in our opinion, to the high efficacy of chemofiltration, demonstrated by a total drug removal of approximately 30% measured in the peripheral venous blood, and confirming the data previously observed in other cancer patients [24, 25].

A significant percentage of patients in this series (approximately 48%) had refused systemic chemotherapy for personal choice or other reasons and another percentage came from countries whose health system did not cover the expenses of systemic chemotherapy in advanced stages of cancer. This is not standard in Italy or Central Europe, but our series included also patients from East Europe and Asia. The high percentage (approximately, 50% in the whole series of 162 patients and approximately 30% in the 43 TNBC patients) of subjects not previously treated with systemic chemotherapy had negative impact on median survivals calculated from the LM diagnosis. This study demonstrated that the MST provided by ITP was lower in the group of patients in which LM were not previously treated with systemic chemotherapy in comparison to those in which the sequence systemic chemotherapy until progression followed by ITP was adopted. This phenomenon was registered both in TNBC patients with LM and in the whole cohort of LM breast cancer patients (Fig. 5a).

The major limitations of this study were: (i) the long time of accrual that started 25 years ago, with difficulty in comparing with current systemic therapies, also in relation to the recent observations about the molecular complexity of TNBC which have determined the registration of many trials with both targeted therapy and new immunotherapy drugs and, consequently, the difficulty in evaluating the ethical applicability to ITP when less invasive treatments are available; (ii) the TNBC patients with LM metastases belong to a highly selected group, which is not representative of all patients with TNBC; (iii) in selected subgroups of TNBC patients with LM evaluated in this study (i.e. patients with malignant pleural effusion or the so-called multiple chronic conditions), there are too few patients for reliable survival analyses.

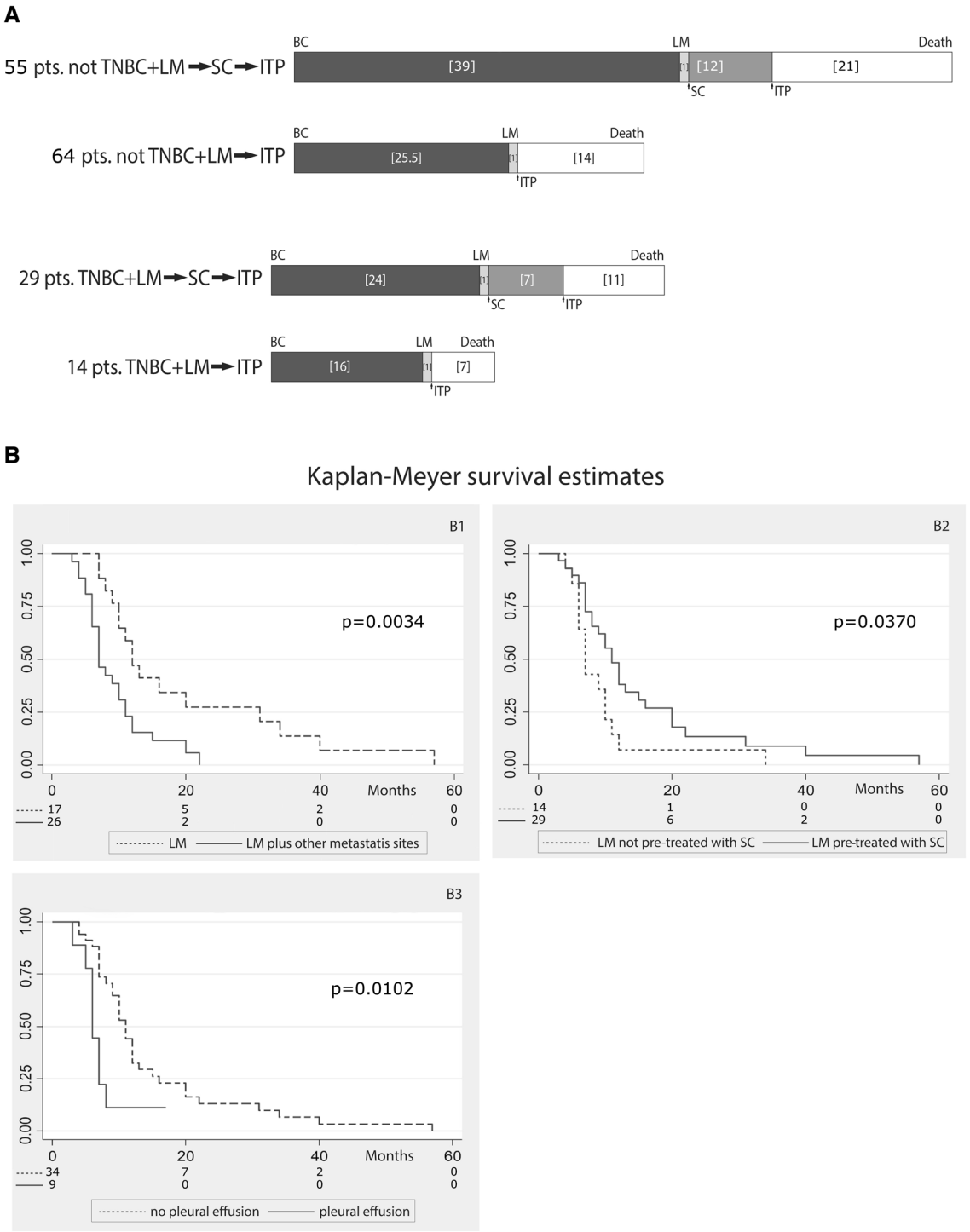

Fig. 5 **a** Horizontal bar histograms of survival. Numbers in brackets are median survival times in months. *Pts* patients, *TNBC* triple-negative breast cancer, *LM* lung metastases, *SC* systemic chemotherapy, *ITP* isolated thoracic perfusion. → treatment. **b** Kaplan–Meier survival curves in TNBC patients with LM treated with ITP (43 cases). *B1* Lung-limited metastatic site versus LM with other metastatic sites. *B2* LM pre-treated with systemic chemotherapy versus LM not pre-treated with systemic chemotherapy. *B3* Absence of malignant pleural effusion versus presence of malignant pleural effusion

In conclusion, ITP was a feasible, safe, and tolerable procedure, providing approximately 50% of responses in patients with lung metastases from breast cancer and MST of 14 months from initial ITP to death or last contact. Moreover, with regard to the sub-group of TNBC patients with LM, the results of this study suggest that the inclusion of ITP in the continuum of cure could offer chances to overcome the drug resistance of metastatic cells and may induce substantial tumour response even if conventional systemic chemotherapy has failed. However, although the present data allow interesting considerations about tolerability and response rates of ITP, they do not allow robust conclusions about survival.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

Research involving human participants and/or animals This retrospective observational study had been conducted in accordance with the ethical standards of the Committee on Human Experimentation, after approval of the Ethics Committee in L'Aquila (n.10/CE/2018), and according to all rules for good clinical practice included in the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. Cardoso F, Costa A, Senkus E et al (2017) 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 31:244–259
2. Senkus E, Łacko A (2017) Over-treatment in metastatic breast cancer. Breast 31:309–317
3. Brackstone M, Fletcher GG, Dayes ISA et al (2015) Locoregional therapy of locally advanced breast cancer: a clinical practice guideline. Curr Oncol 22(Suppl 1):S54–S66. https://doi.org/10.3747/co.22.2316
4. Gennari A, Stockler M, Puntoni M et al (2011) Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 29:2144–2149
5. Foulkes WD, Smith IE, Reis-Filho JS (2010) Triple-negative breast cancer. N Engl J Med 363:1938–1948
6. Zeichner SB, Terawaki H, Gogineni K (2016) A review of systemic treatment in metastatic triple-negative breast cancer. Breast Cancer Basic Clin Res 10:25–63
7. Aigner KR, Guadagni S, Zavattieri G (2016) Regional chemotherapy for thoracic wall recurrence and metastasized breast cancer. In: Aigner KR, Stephens FO (eds) Induction chemotherapy. Systemic and locoregional. Springer-Verlag, Berlin, pp 173–186
8. Guadagni S, Clementi M, Valenti M et al (2006) Thoracic stopflow perfusion in the treatment of refractory malignant pleural mesothelioma: a phase I-II evaluation/trial. In Vivo 20:715–718
9. Aigner KR, Selak E, Gailhofer S (2017) Isolated thoracic perfusion with chemofiltration for progressive malignant pleural mesothelioma. OncoTargets Ther 10:3049–3057
10. Guadagni S, Muller H, Valenti M et al (2004) Thoracic stopflow perfusion in the treatment of refractory non-small cell lung cancer. J Chemother 16(5):40–43
11. Ruscitti C, Guadagni S, Russo F et al (2009) Thoracic stopflow perfusion for refractory lymphoma: a phase I-II evaluation trial. In Vivo 23:447–458
12. Muller H, Guadagni S (2008) Regional chemotherapy for carcinoma of the lung. Surg Oncol Clin N Am 17:895–917
13. Varrassi G, Guadagni S, Ciccozzi A et al (2004) Hemodynamic variations during thoracic and abdominal stop-flow regional chemotherapy. Eur J Surg Oncol 30:377–383
14. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response valuation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
15. Guadagni S, Fiorentini G, Clementi M, Palumbo P, Mambrini A, Masedu F (2017) Mitomycin C hypoxic pelvic perfusion for unresectable recurrent rectal cancer: pharmacokinetic comparison of surgical and percutaneous techniques. Updates Surg 69:403–410. https://doi.org/10.1007/s13304-017-0480-6
16. Zhang Y, Huo M, Zhou J, Xie S (2010) PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Progr Biomed 99:306–314
17. Tseng LM, Hsu NC, Chen SC et al (2013) Distant metastasis in triple-negative breast cancer. Neoplasma 60:290–294
18. Gadiyaram VK, Kurian S, Abraham J et al (2010) Recurrence and survival after pulmonary metastasis in triple-negative breast cancer. J Clin Oncol 28:15s. https://doi.org/10.1200/jco.2010.28.15_suppl.1131 **(suppl; abstract 1131)**
19. Rugo HS, Barry WT, Moreno-Aspitia A et al (2015) Randomized phase III study of paclitaxel once per week compared with nanoparticle albumin-bound Nab-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (alliance). J Clin Oncol 33:2361–2369
20. Kaufman PA, Awada A, Twelves C et al (2015) Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 33:594–601
21. Maeda S, Saimura M, Minami S et al (2017) Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Breast 32:66–72
22. Wahba HA, El-Hadaad HA (2015) Current approaches in treatment of triple-negative breast cancer. Cancer Biol Med 12:106–116
23. Tutt A, Ellis P, Kilburn L, et al (2015) The TNT trial: A randomized phase III trial of carboplatin © compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) [abstract]. In: Proceedings of the thirty-seventh annual CTRC-AACR San Antonio breast cancer symposium: 2014 Dec 9–13; San Antonio, TX. Philadelphia (PA): AACR. Cancer Res 75 (9 Suppl): Abstract nr S3-01
24. Fiorentini G, Poddie DB, Cantore M et al (2004) Hepatic intra-arterial chemotherapy (HIAC) of high dose mitomycin and

epirubicin combined with caval chemofiltration versus prolonged low doses in liver metastases from colorectal cancer: a prospective randomised study. J Chemother 16:51–54

25. Guadagni S, Clementi M, Valenti M et al (2007) Hypoxic abdominal stop-flow perfusion in the treatment of advanced pancreatic cancer: a phase II evaluation/trial. Eur J Surg Oncol 33:72–78