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Facoltà di Medicina e Chirurgia

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Coordinatore: ***Prof. Aldo Gerbino***

CISPLATIN (C) AND ALIMTA (A) WITH PANITUMUMAB FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NS-NSCLC): A PHASE I-DOSE FINDING STUDY.

PhD Thesis by:
Dr. Laura Palmeri

Tutor:
Dr. Fabio Fulfaro

Course Coordinator:
Prof. Aldo Gerbino

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1. ABSTRACT

Background

The treatment of NSCLC is rapidly changing since new drugs are becoming available. Recently, CA has become a standard for the first line treatment of NS-NSCLC.

Previous clinical studies have shown that anti-EGFR MoAb may be added to chemotherapy, but the identification of a molecular signature can predict their activity and better define their true role.

Aims

In absence of data about the MTD of Panitumumab (a MoAb targeting the EGFR, potentially active in NS-NSCLC) when associated to chemotherapy, we decided to assess the optimal dose of panitumumab in combination with CA. Moreover, in view of a future phase II study, all pts will be studied for the following molecular characteristics: EGFR gene copy number (FISH); EGFR IHC; KRAS, BRAF, PI3KCA mutational status; ERCC1 and TS genes polymorphisms analysis. A particular attention will be paid to their possible correlation with outcome.

Materials and methods

Eligible patients must have: histological diagnosis of previously untreated, Stage IIIb or IV, NS-NSCLC, EGFR + (FISH).

A minimum of 6 to a maximum of 18 patients have to be treated with panitumumab at escalating doses (i.e. the first 3 patients at 5.5 mg/kg q3w, than in absence of dose limiting toxicities (DLT) the next 3 patients at 7.2 mg/kg q3w, than in absence of DLT toxicities the next 3 patients at 9 mg/kg q3w) in association with CDDP and at standard doses.

Activity and tolerability have been evaluated in terms of response rate and NCI-CTC v. 3.0.

Results

At the time of writing 8 patients have been screened for EGFR overexpression and 4 resulted eligible. None of the 3 patients treated with the first dose experienced a DLT, then the fourth patient is currently being treated with the second dose (7.2 mg/kg). One partial response and two disease stabilization have been

obtained, so far.

Conclusions

These very preliminary results have so far showed that panitumumab (at the present dose) can be safely associated with CA in NS-NSCLC patients. The study is currently on going.

2. INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause for cancer death among men and women in the US[1].
In Italy, between 2003 and 2005, lung cancer resulted the 3rd most frequent tumor among men (13,1% of all tumors), and the 4th among women (5% of all tumors), whereas it represents the leading cause for cancer-specific death in men (27,6%) and the 3rd cause among women (10,3%)[2].
The NSCLCs include three main histotypes: squamous cell carcinoma, adenocarcinoma and large-cell or undifferentiated carcinoma. In Italy, in 2008, it has been estimated that the national incidence of each of the considered NSCLC histological subtypes was: adenocarcinoma 33.9% in males and 46.1% in females; squamous cell carcinoma 28.5% in males and 16% in females; large cell carcinoma 2.6% in males and 2.9% in females[3, 4].
The treatment strategy is highly dependent upon the stage of the disease: surgery represents the gold standard in the early stages, multimodality treatments are used for managing locally advanced disease, and palliative chemotherapy is the standard of care for metastatic disease[5]. In fact, about 40% of patients have metastatic disease at the time of diagnosis, so that the efforts of the clinicians are directed to ameliorate and innovate the treatment options for such population.
Chemotherapy has become the standard treatment for metastatic NSCLC patients since, in 1995, the NSCLC Collaborative Group demonstrated that platinum-based chemotherapy provided a modest, even though significant, survival benefit and a significant improvement of the quality of life (QoL) over the best supportive care[6]. A substantial equivalence in terms of efficacy, with different tolerability profiles, have been demonstrated between cis- and carboplatin, in the CISCA meta-analysis published by Ardizzoni et al[7]. In the last few years a significant correlation has been found among the expression and the polymorphysms of ERCC1 gene and the response to platinum compounds[8, 9].

Since the early 90s, various new 3rd generation drugs – i.e. vinorelbine, gemcitabine, paclitaxel, docetaxel – demonstrated to be active for the treatment of advanced NSCLC patients with no significant differences among them in terms of efficacy and minimal changes in tolerability[10-14].
In the last years, new broadly active agents with refined mechanisms of action have become available for NSCLC treatment.
Alimta (A) is a novel folate-based anticancer compound with a broad spectrum of activity against human tumor cell lines, it predominantly inhibits thymidylate synthase (TS), but is also active against the folate enzymes involved in the *de novo* synthesis of purines and pyrimidines, including dihydrofolate reductase (DHFR) and glycinamide ribonucletide formyl transferase (GARFT).
Several phase II studies have been carried out on A as single-agent treatment or as a part of platinum-based as well as platinum free combinations, with encouraging results[15-18].
In 2008, the results of a large, international phase III study comparing the association of cisplatin and gemcitabine (CG) versus cisplatin and (CA) for the 1st line treatment of NSCLC have been published[19]. Patients received cisplatin 75 mg/m2 on day 1 and gemcitabine 1250 mg/m2 on days 1 and 8 (n = 863) or cisplatin 75 mg/m2 and 500 mg/m2 on day 1 (n = 862) every 3 weeks for up to six cycles. The primary outcome was overall survival (OS) between treatment arms using a non-inferiority design. With regard to the whole patients population, OS for CA was non-inferior to CG (mOS, 10.3 vs 10.3 months, respectively; HR = 0.94; 95% CI 0.84 to 1.05). Interestingly, when performing the pre-planned histologically-based subgroup analysis OS was statistically superior for CA versus CG in patients with adenocarcinoma (12.6 vs 10.9 months, respectively, 0.84; 95% CI 0.71 to 0.99; p = 0.03) and large-cell carcinoma histology (10.4 v 6.7 months, respectively, 0.67; CI 95% 0.48 to 0.96; p = 0.03); similarly a nearly statistically significant improvement in median PFS was observed according to histology (CA median PFS 5.3 months, 95% CI 4.8-5.7; CG median PFS 4.7 months, 95% CI 4.4-5.4; CA v CG

Adjusted HR 0.90; 95% CI 0.79- 1.02). On the contrary, in patients with squamous cell histology, there was an improvement in survival with CG vs. CA (10.8 vs 9.4 months, respectively, 1.23; 1.00 to 1.51; p = 0.05). Regarding the tolerability profile, the rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia (p </= 0.001); febrile neutropenia (p = 0.002); and alopecia (p < 0.001) were lower, and grade 3 or 4 nausea (p = 0.004) higher in the CA group.

On the basis of such experience, A received the regulatory authorities approval in combination with cisplatin for the first line treatment of NSCLC both in the US and in Europe.

As already mentioned, A inhibits a number of enzyme systems, including DHFR, GARFT, and the bottom one TS, which are of paramount importance in tumour cell DNA synthesis: by blocking TS, A will finally inhibit tumour cell DNA synthesis[20, 21]. It has been found that squamous cell carcinomas have a significantly higher level of TS than adenocarcinomas[22]. This could be meaningful, because patients with low TS levels in their tumours (mainly adenocarcinomas and large cell-carcinoma) are more sensitive to the TS blocking effect of A. Evaluating the polymorphisms of the promoting region of *TS gene,* could be helpful in defining mRNA expression levels of *TS.*

EGFR is a cell surface protein, overexpressed in many cancer types, with a role as prognostic and/or predictive factor associated with resistance and/or sensitivity to anticancer therapies[23]. The autocrine or paracrine stimulation of EGFR by its ligands may have a critical role in the progression of tumors expressing this receptor, and it has been hypothesized that the inhibition of this pathway may inhibit tumor cells survival, proliferation, and metastatic process activation. The receptor drives tumor metastasis and proliferation by binding the ligands EGF, TGF-α, amphiregulin, betacellulin, epiregulin, and/or heparin-binding EGF, which leads to dimerization, autophosphorylation and activation of the receptor and the subsequent activation of at least three downstream intracellular signaling pathways: the Ras-Raf-MAPK pathway, the

PI3K-Akt pathway, and the protein kinase C-Jak/Stat pathway[24].
There are actually 3 main methods of testing for EGFR[25-27]: the first is testing for the gene itself with mutational screening (by polymerase chain reaction or by DNA sequencing), and this is the most consistent way to identify patients who are extremely likely to benefit from EGFR tyrosine kinase inhibitors (TKIs). The next is EGFR gene copy number and amplification, which is tested by fluorescence in situ hybridization (FISH) and has been investigated in several studies. It is not as clearly or consistently predictive as mutational screening though still may have some value. The last method tests for EGFR protein levels on the cancer cells via immunohistochemistry (IHC).
A key area of debate is the relationship between EGFR mutation, increased EGFR gene copy number, EGFR protein expression, and outcome after treatment with EGFR inhibitors, i.e. TKIs and monoclonal antibodies (mab). Two large, randomized clinical trials of EGFR TKI monotherapy in second-/third-line NSCLC have been retrospectively analysed for biomarkers that may predict response and survival benefit to EGFR TKIs: BR.21[28-30] and ISEL[25, 31, 32]. Data from both trials supported EGFR FISH status as a potential predictive marker of clinical outcome to TKIs both in terms of tumor response and patient survival. Moreover, a recent detailed biomarker analysis of a large phase III study highlighted some important points. The investigators looked at *EGFR* gene copy number, *EGFR* mutation status, and EGFR IHC expression and found a lot of overlap between IHC, *EGFR* mutations, and *EGFR* gene copy numbers[33]. Moreover, although EGFR mutation testing is available for clinical use, the current 7- to 14-day time frame may limit the usefulness of the test, so that EGFR copy number FISH evaluation could be used to achieve a faster evaluation[34, 35]. A recent report by Dacic et al analyzed the morphological and clinicopathological characteristics of 345 surgically treated primary lung adenocarcinomas with respect to their EGFR and KRAS mutational profile and EGFR FISH status. They found EGFR FISH positivity, as defined by the Colorado criteria, as a significant

predictor of EGFR mutations, with high polysomy as the strongest predictive criterion[36]. To date, however, for anti-EGFR monoclonal antibody, no certain data exist on the predictive value of EGFR related biomarkers as they only come from retrospective analysis[26, 37-39].

With regards to anti-EGFR mabs, cetuximab, directed against EGFR has been approved in the US on the basis of the results of the FLEX study, in which they investigated the value of adding cetuximab to the combination of cisplatin and vinorelbine. This study was conducted in Europe and enrolled more than 1100 patients who were all tested by IHC for EGFR positivity, although it was a very lenient definition of EGFR positivity with just a single cell being enough to allow patients to be enrolled[37]. The primary endpoint, OS, was statistically significantly better in favor of cetuximab with chemotherapy, but the median survival difference was only 1.2 months (11.3 months vs 10.1 months). And because of this, there has been a lot of discussion about whether these results are really clinically significant, and one of the hopes has been that we might find a subgroup of patients who are far more likely to benefit meaningfully from cetuximab. Recently, there was a presentation of results as a function of whether patients had high EGFR expression or low EGFR expression, the definition being a product of the intensity of staining and the proportion of cancer cells that are positive[38]. Approximately one third of the patients had high EGFR expression. Looking at the median OS for high EGFR expression and low EGFR expression and comparing them for chemotherapy plus cetuximab vs chemotherapy alone, it was 9.8 for chemotherapy plus cetuximab and 10.3 for chemotherapy alone, whereas in the high EGFR expression it was 12 months for chemotherapy plus cetuximab and 9.6 months for chemotherapy alone. This suggests that there could be a meaningful way to select patients far more likely to benefit in the range of 2 or more months and not pursue this for other patients.

Panitumumab is a high affinity human IgG2 monoclonal antibody directed against human EGFR[40]. Panitumumab blocks EGFR

binding of the ligands EGF, TGF, amphiregulin, betaregulin, epiregulin, and heparin-binding EGF.
In vitro studies demonstrated that treatment with panitumumab inhibited ligand-induced EGFR autophosphorylation and EGFR dependent cellular response, including extracellular acidification, cell proliferation, and production of angiogenic factors by tumor cells. Panitumumab alone demonstrated to be able to eradicate established xenograft A431 epidermoid carcinoma tumors and inhibit tumor growth of breast, renal, pancreatic, head and neck, prostate, ovarian, and NSCLC. Combination of panitumumab and chemotherapeutic agents resulted in greater inhibition of tumor growth in colon, lung, breast, ovarian, pancreas, and head and neck xenograft tumors than either agent alone. Panitumumab with radiotherapy also resulted in increased inhibition of head and neck and lung cancer tumor xenografts. These results indicate that panitumumab may play a therapeutic role in the treatment of multiple EGFR expressing human solid tumors[40-42].
To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN.
Data from multiple clinical trials of panitumumab in CRC have demonstrated that patients whose tumors contain activating mutations in the KRAS gene do not derive clinical benefit from antibody therapy and have significantly shortened survival compared to patients whose tumor expresses wild-type KRAS[43, 44], whereas no certain data are available with regard to NSCLC patients.
No clear additive effects were observed in the NSCLC setting when panitumumab was combined with carboplatin/paclitaxel. The preliminary and updated results of this phase II randomized study have not shown significant differences in response rate, time to progression and overall survival favouring panitumumab receiving patients[41]. One concern about this trial is that patient population was unselected. Identification of a molecular signature predicting benefit from anti-EGFR antibodies might be helpful in defining their true role in the treatment of such patients.

In absence of data about the Maximum Tolerable Dose of panitumumab when associated to chemotherapy, we decided to assess the optimal dose of panitumumab in combination with the combination cisplatin-alimta (CA). Moreover, in view of a future phase II study, all pts will be studied for the following molecular characteristics: EGFR gene copy number (FISH); EGFR IHC; KRAS, BRAF, PI3KCA mutational status; ERCC1 and TS genes polymorphisms analysis. A particular attention will be paid to their possible correlation with outcome.

3. AIMS OF THE THESIS

Primary Objective: to assess the MTD dose of panitumumab in combination with CA.

Secondary objectives:

- Overall Response Rate (ORR), calculated as the sum of complete and partial tumour responses observed, divided by the number of evaluable patients.
- Tolerability, evaluated on the total number of patients receiving at least one cycle of treatment according to NCI-CTC v3.0.
- The following molecular characteristics - EGFR gene copy number (FISH); EGFR IHC; KRAS, BRAF, PI3KCA mutational status; ERCC1 and TS genes polymorphisms analysis – will be collected.

4. MATERIALS AND METHODS

4.1 INCLUSION CRITERIA

- Histological diagnosis of previously untreated, non-squamous, NSCLC, EGFR FISH +
- Stage IIIb or IV
- Age 18-75; (for elderly pts, > 70 aa, "Comprehensive Geriatric Assessment" must be performed)
- PS ECOG 0-1
- At least 1 measurable lesion (RECIST)
- Haematology:
  - Neutrophil count ≥1.5x109/L
  - Platelet count ≥100x109/L
  - Leucocyte count > 3,000/mm
  - Hemoglobin ≥ 9 g/dL
- Hepatic Function:
  - Total bilirubin ≤ 1.5 time the upper normal limit (UNL)
  - ASAT ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
  - ALAT ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
- Renal Function: serum creatinine ≤1.5xUNL
- Metabolic Function
  - Magnesium ≥ lower limit of normal.
  - Calcium ≥ lower limit of normal.

- Written informed consent.
- Geographical accessibility to the participating center and compliance with treatment and scheduled follow-up.

4.2 EXCLUSION CRITERIA

- Previous (within 5 years of study entry) or concurrent neoplasm other than adequately managed in situ carcinoma of the cervix and/or basal cell skin cancer
- Clinically detectable brain metastases

- Concurrent treatment with other chemotherapeutic, hormonal or biologic antineoplastic agents.
- Prior exposure to cisplatin in the adjuvant setting
- Previous chemotherapy for metastatic disease
- Previous radiotherapy
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) ☐ 1 year before enrollment/randomization
- History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline chest CT scan.
- Subject pregnant or breast feeding, or planning to become pregnant within 6 months after the end of treatment.
- Subject (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment.

4.3 PRETREATMENT EVALUATION

Before enrolment the following procedures must be carried out and the samples collected:

- Complete history and physical examination, ECOG PS;
- EKG, echocardiography, blood pressure;
- blood cell count (BCC) and serum chemistry tests;
- CEA, Ca 19.9, NSE, Cyfra 21.1 (optional);
- chest X rays;
- bone scan;
- CT scan of the brain, chest and abdomen;
- a 10 cc EDTA blood sample stored at 20°C. Subsequently sent in dry ice to the centralized lab;
- five 8-10 micron tumor slices in Eppendorf tubes, (DNA extraction and mutational analysis) and three slides (section of 2-3 micron) for the FISH analysis.

- Other exams will be performed as needed.

4.4 STUDY DESIGN

The treatment schedule include:
- CDDP 75 mg/m2 d1 q21 (min 2 - max 6 cycles)
- Alimta 500 mg/m2 d1 q21 (min 2 - max 6 cycles), with standard pre-medication.

As regards panitumumab dose, it is administered to successive patient cohorts in a dose-escalating fashion to identify the MTD using a traditional three or six patient-per-cohort design. The starting and maximum doses have been calculated based on on previous phase I/II studies of panitumumab.

The dose-finding study should be performed in a minimum of 6 to a maximum of 18 patients (i.e. the first 3 patients at 5.5 mg/kg q3w, than in absence of dose limiting toxicities (DLT) the next 3 patients at 7.2 mg/kg q3w, than in absence of DLT the next 3 patients at 9 mg/kg q3w; in any case, the phase I study will be stopped after the first cohort treated at 9 mg/kg) (fig.1). The minimum lenght of observation will be at least of two cycles.

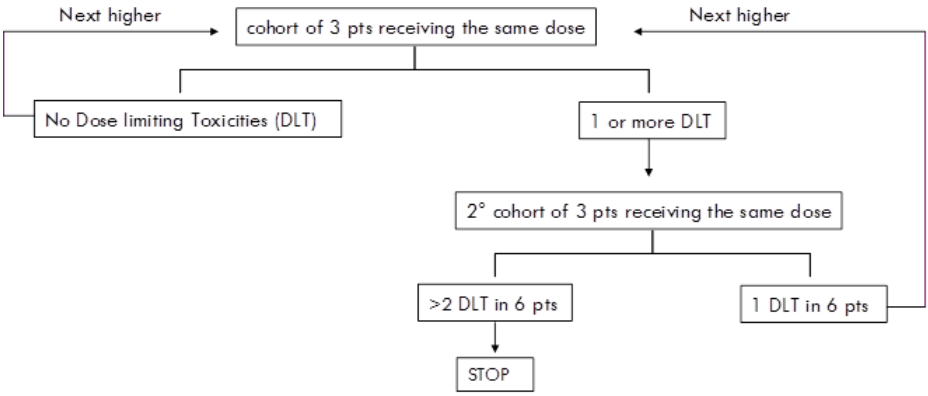

Figure 1. Study flow chart

Toxicity evaluation

Toxicities is recorded and graded at each administration according to the NCI CTC vs 3 criteria. Non-hematologic toxicity of each cycle is assessed before the start of the next cycle. The worst toxicity encountered during the whole treatment is reported for each patient.

It is important to be noted that, when escalating Panitumumab dose only DLT specific for Panitumumab, i.e. G4 Gastrointestinal disorders (diarrhea, nausea, vomiting); G3/4 general disorders (fatigue, infusion reactions, pyrexia and chills, mucosal inflammation); G4 metabolism and nutrition disorders (hypomagnesemia, hypocalcemia, hypokalemia, dehydration); G3/4 nervous system disorders (headhache), G3/4 respiratory disorders (cough, dyspnea); G4 skin and eye disorders (dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, dry skin, skin fissures, paronychia, irsutism, hypertricosis, conjunctivitis, growth of eyelashes, increased lacrimation, dry eye, ocular hyperemia, nasal dryness, nasal bleeding, stomatitis, dry mouth, chapped lips) G3/4 vasculars disorders (pulmonary embolism) are considered as DLT. Nevertheless, if G3-4 toxicities not commonly considered as attributable to the chemotherapeutic agents (cisplatin, alimta) are observed, these should be considered as related to panitumumab and then as DLTs.

The panitumumab total dose is calculated based on the subject's actual body weight at baseline and could not be re-calculated unless the actual body weight changes by at least 10%.

Panitumumab should be continued until progressive disease/unacceptable toxicity/patient's refusal/death occur.

Clinical assessment

After the administration of 2 cycles, patients will undergo restaging of the disease:

- If progression of disease occurs, the treatment will stopped and the patient will be followed up for survival; investigators will be free of giving any further antitumor treatment according to each

partecipating centre practice.

- in case of a complete response (CR), partial response (PR) or stable disease (SD), patients will receive further 2 cycles of chemotherapy; a maximum of 6 cycles is planned; panitumumab will be continued until progressive disease/unacceptable toxicity/patient's refusal/death occur.

Statistical analysis

This is a phase I safety and tolerability trial conducted to determine the MTD of panitumumab in association with cisplatin and alimta. The sample size was based on the standard phase I design of toxicity assessment. In addition, tumor response and biological features are evaluated as secondary objectives as the proportion of patients experiencing radiologically confirmed response and the proportion of patients with every molecular feature, respectively. For the safety analysis, incidence rates of grade 3/4 adverse events (DLT), drug-related adverse events, and hematologic/biochemical toxicities are reported based on National Cancer Institute Common Toxicity Criteria version 3 by dose level.

5. RESULTS

Since September 2011 8 patients have been screened for enrolment and 4 have been excluded because of the absence of EGFR FISH amplification. All of the 4 patients included until now have been treated with at least one dose of the drug, and can be included in the safety analysis, whereas only 3 patients are evaluable for response to date. Patient characteristics at baseline are summarized in Table 1.

Table 1. Patient baseline characteristics

Characteristic	**n**
Total patients	4
Sex	
Male	3
Female	1
Age	
Median	60 y
Range	53-66
ECOG PS	
0	3
1	1
Tumor Histology	
Adenocarcinoma	3
Large cell carcinooma	1
EGFR FISH +	4
N° of metastatic sites	
1 - 2	3
>2	1

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

The first 3 patients have been treated at the first dose level (i.e. 5.5 mg/kg, with no observation of the G3/4 panitumumab-related adverse events described above (DLT), so that the fourth patient is currently been treated at the next dose level (i.e. 7.2 mg/kg).

Table 2. Summary of the results per patient

Patient 1	
Sex	Male
Age	66
PS	1
Dose level	5.5 mg/kg
N° of cy	2
Best response	SD
DLT	No
Patient 2	
Sex	Male
Age	63
PS	0
Dose level	5.5 mg/kg
N° of cy	6 cy + 4 M
Best response	PR
DLT	No
Patient 3	
Sex	Male
Age	57
PS	0
Dose level	5.5 mg/kg
N° of cy	6 cy
Best response	SD
DLT	no
Patient 4	
Sex	Female
Age	53
PS	0
Dose level	7.2 mg/kg
N° of cy	1 cy
Best response	NE
DLT	No

PS, performance status; N°, number; cy, cycle; SD, stable disease; DLT, dose limiting toxicity; M, maintenance; PR, partial response; NE, not evaluated.

As regards tumor response, patient number 1 achieved stable disease (SD) after 2 cycles but experienced clinical progression of the disease after the third cycle that lead to treatment discontinuation; patient number 2 achieved a partial response after 2 cycles and subsequent SD lasting more than 6 months, and is currently being treated with panitumumab maintenance; patient number 3 achieved SD after two cycles, that was confirmed after 4 cycles, but progressive disease recently occurred after the 6th cycle administration.

6. DISCUSSION

NSCLC is among the leading causes of cancer death in the Western countries. The treatment of NSCLC is rapidly changing since new drugs are becoming available and quite recently, the doublet cisplatin-alimta has become a standard for the first line treatment of NS-NSCLC.
EGFR is a cell surface protein, with a significant role as a prognostic and/or predictive factor, deeply involved in the progression of tumors expressing this receptor. It has been proved that the inhibition of this pathway may inhibit tumor cells survival and proliferation, in certain patient population. There are two main classes of EGFR inhibitor that have been experimented in the treatment of NSCLC: TKIs and mab.
A key area of debate is the relationship between EGFR mutation, increased EGFR gene copy number, EGFR protein expression, and outcome after treatment with EGFR inhibitors. EGFR protein expression assessed by IHC, EGFR gene copy number assessed by FISH, and mutations in the EGFR or other downstream genes, have been under investigation as potential biomarkers that may predict sensitivity to anti-EGFR therapy [25, 28-32]. Data from these trials supported EGFR FISH status as a potential predictive marker of clinical outcome of patients treated with anti-EGFR agents. To date, however, for anti-EGFR monoclonal antibody, no certain data exist on the predictive value of EGFR related biomarkers as they only come from retrospective analysis [26, 37-39].
Panitumumab is a high affinity human IgG2 monoclonal antibody directed against human EGFR [40].
Previous studies demonstrated that panitumumab alone or in combination with chemotherapeutic or targeted agents or radiation may play a therapeutic role in the treatment of multiple EGFR expressing human solid tumors [40-42].
To date, panitumumab has been evaluated in combination with chemotherapy in subjects with CRC, NSCLC, and SCCHN. In the NSCLC setting when panitumumab was combined with

carboplatin/paclitaxel no beneficial effect has been observed, with no significant differences in activity and/or efficacy vs carboplatin/paclitaxel alone [41]. One concern about this trial is that patient population was unselected, as that of the FLEX trial [37, 38].

Therefore, our study is aimed to assess the optimal dose of panitumumab to be combined with cisplatin and alimta for the treatment of patients affected by advanced non-squamous NSCLC (EGFR FISH+). Morever, the identification of a molecular signature predicting benefit from anti-EGFR antibodies might be helpful in defining their true role in the treatment of such patients.

Our very preliminary results demonstrated panitumumab in combination with CA to be safe in such population of patients at the first dose (5.5 mg/kg), with no DLT observed to date and one patient currently being treated at the higher dose (7.2 mg/kg).

Due to the very small small sample enrolled to date, no definitive conclusion can be drawn, but the results in terms of response are encouraging as those of tolerability.

Very interesting data are expected to be collected with regard to moleculare characteristic of these subjects and the possible correlation with various outcome measures.

7. CONCLUSIONS

These are very preliminary results. Panitumumab 5.5 MG/KG can be safely associated with CA in NS-NSCLC EGFR FISH + patients, achieving a good disease control rate. No definitive conclusion can be drawn since the study is currently on going.

8. REFERENCES

1. SEER, *SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.* 2011.
2. AIRTWorkingGroup, *I nuovi dati di incidenza e mortalità - Periodo 2003-2005.* Epidemiologia & Prevenzione, 2009: p. e9-15.
3. Curado, M.P., et al., *Cancer Incidence in Five Continents, Vol. IX*. Vol. 160. 2007, Lyon: IARC Scientific Publications.
4. Banca Dati dell'Associazione Italiana Registro Tumori, F., *Stima del numero di casi incidenti e prevalenti di tumore del polmone non a piccole cellule, per istotipo, nelle regioni italiane.* Giornale Italiano di Health Technology Assessment, 2008. **1**(1): p. 15-20.
5. Thatcher, N., *First- and second-line treatment of advanced metastatic non-small-cell lung cancer: a global view.* BMC Proc, 2008. **2 Suppl 2**: p. S3.
6. *Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group.* Bmj, 1995. **311**(7010): p. 899-909.
7. Ardizzoni, A., et al., *Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis.* J Natl Cancer Inst, 2007. **99**(11): p. 847-57.
8. Viguier, J., et al., *ERCC1 codon 118 polymorphism is a predictive factor for the tumor response to oxaliplatin/5-fluorouracil combination chemotherapy in patients with advanced colorectal cancer.* Clin Cancer Res, 2005. **11**(17): p. 6212-7.
9. Cobo, M., et al., *Customizing cisplatin based on quantitative excision repair cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer.* J Clin Oncol, 2007. **25**(19): p. 2747-54.
10. Delbaldo, C., et al., *Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis.* Jama, 2004. **292**(4): p. 470-84.
11. Fossella, F., et al., *Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group.* J Clin Oncol, 2003. **21**(16): p. 3016-24.
12. Kelly, K., et al., *Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial.* J Clin Oncol, 2001. **19**(13): p. 3210-8.
13. Scagliotti, G.V., et al., *Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer.* J Clin Oncol, 2002. **20**(21): p. 4285-91.
14. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 92-8.
15. Clarke, S.J., et al., *Phase II trial of pemetrexed disodium (ALIMTA, LY231514) in chemotherapy-naive patients with advanced non-small-cell lung cancer.* Ann Oncol, 2002. **13**(5): p. 737-41.
16. Rusthoven, J.J., et al., *Multitargeted antifolate LY231514 as first-line chemotherapy for patients with advanced non-small-cell lung cancer: A phase II study. National Cancer Institute of Canada Clinical Trials Group.* J Clin Oncol, 1999. **17**(4): p. 1194.
17. Comella, P., et al., *Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer A randomized phase II SICOG trial.* Lung Cancer, 2009.
18. Shepherd, F.A., et al., *Phase II study of pemetrexed disodium, a multitargeted antifolate, and cisplatin as first-line therapy in patients with advanced nonsmall cell lung carcinoma: a study of the National Cancer Institute of Canada Clinical Trials Group.* Cancer, 2001. **92**(3): p. 595-600.
19. Scagliotti, G.V., et al., *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol, 2008. **26**(21): p. 3543-51.

20. Eismann, U., et al., *Pemetrexed: mRNA expression of the target genes TS, GARFT and DHFR correlates with the in vitro chemosensitivity of human solid tumors.* Int J Clin Pharmacol Ther, 2005. **43**(12): p. 567-9.
21. Hanauske, A.R., et al., *In vitro chemosensitivity of freshly explanted tumor cells to pemetrexed is correlated with target gene expression.* Invest New Drugs, 2007. **25**(5): p. 417-23.
22. Ceppi, P., et al., *Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase.* Cancer, 2006. **107**(7): p. 1589-96.
23. Nicholson, R.I., J.M. Gee, and M.E. Harper, *EGFR and cancer prognosis.* Eur J Cancer, 2001. **37 Suppl 4**: p. S9-15.
24. Mendelsohn, J. and J. Baselga, *Epidermal growth factor receptor targeting in cancer.* Semin Oncol, 2006. **33**(4): p. 369-85.
25. Hirsch, F.R., et al., *Epidermal growth factor receptor immunohistochemistry: comparison of antibodies and cutoff points to predict benefit from gefitinib in a phase 3 placebo-controlled study in advanced nonsmall-cell lung cancer.* Cancer, 2008. **112**(5): p. 1114-21.
26. Hirsch, F.R., et al., *Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy.* J Clin Oncol, 2008. **26**(20): p. 3351-7.
27. Lynch, T.J., et al., *Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.* N Engl J Med, 2004. **350**(21): p. 2129-39.
28. Liu, G., et al., *Pharmacogenetic Analysis of BR.21, a Placebo-Controlled Randomized Phase III Clinical Trial of Erlotinib in Advanced Non-small Cell Lung Cancer.* J Thorac Oncol, 2012. **7**(2): p. 316-22.
29. Wheatley-Price, P., et al., *Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21.* J Clin Oncol, 2008. **26**(14): p. 2350-7.
30. Zhu, C.Q., et al., *Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21.* J Clin Oncol, 2008. **26**(26): p. 4268-75.
31. Hirsch, F.R., et al., *Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer.* J Clin Oncol, 2006. **24**(31): p. 5034-42.
32. Thatcher, N., et al., *Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer).* Lancet, 2005. **366**(9496): p. 1527-37.
33. Fukuoka, M., et al., *Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS).* J Clin Oncol, 2011. **29**(21): p. 2866-74.
34. Varella-Garcia, M., et al., *EGFR fluorescence in situ hybridisation assay: guidelines for application to non-small-cell lung cancer.* J Clin Pathol, 2009. **62**(11): p. 970-7.
35. Lynch, T.J., et al., *Summary statement: novel agents in the treatment of lung cancer: advances in epidermal growth factor receptor-targeted agents.* Clin Cancer Res, 2006. **12**(14 Pt 2): p. 4365s-4371s.
36. Dacic, S., et al., *Clinicopathological predictors of EGFR/KRAS mutational status in primary lung adenocarcinomas.* Mod Pathol, 2010. **23**(2): p. 159-68.
37. Pirker, R., et al., *Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial.* Lancet, 2009. **373**(9674): p. 1525-31.
38. Pirker, R., et al., *EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study.* Lancet Oncol, 2012. **13**(1): p. 33-42.
39. Khambata-Ford, S., et al., *Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer.* J Clin Oncol. **28**(6): p. 918-27.
40. Yang, X.D., et al., *Eradication of established tumors by a fully human monoclonal antibody to the epidermal growth factor receptor without concomitant chemotherapy.* Cancer Res, 1999. **59**(6): p. 1236-43.
41. Crawford J, e.a., *ABX-EGF in combination with paclitaxel and carboplatin in advanced non small-cell lung cancer (NSCLC).* JCO, 2004. **22**: p. 7083a.

42. Weiner, L.M., et al., *Dose and schedule study of panitumumab monotherapy in patients with advanced solid malignancies.* Clin Cancer Res, 2008. **14**(2): p. 502-8.
43. Amado, R.G., et al., *Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.* J Clin Oncol, 2008. **26**(10): p. 1626-34.
44. Lievre, A., et al., *KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab.* J Clin Oncol, 2008. **26**(3): p. 374-9.

Curriculum Vitae	
Personal information	
First name / Surname	**Laura Palmeri**
Address	Via Francesco Caracciolo, 30 20155 Milan Italy
E-mail	laura.palmeri@gmail.com
Nationality	Italian
Date and place of birth	11/03/1980, Palermo
Work experience	
Dates	Since 15/09/2010 until now
Occupation or position held	Consultant Medical Oncologist
Main activities and responsibilities	AS a Medical Oncologist, at the Falck Oncology Ward, she predominantly sees patients undergoing investigations, chemotherapy, radiotherapy or supported care for various solid cancers. Her current interests include the management and molecular biology of lung and head and neck cancers. As co-investigator, she is involved in a number of GCP Clinical Trials.
Name and address of employer	Falck Division of Medical Oncology at Niguarda Ca' Granda Hospital Piazza Ospedale Maggiore, 3 20162 Milan Italy
Type of business or sector	Medical Oncology
Education and training	
Dates	Since 01/03/2009 until 31/12/2011
Title of qualification	Research Doctorate in Clinical and Experimental Oncology
Principal subjects/occupational skills covered	During her fellowship her interests are being focused on molecular aspects and clinical mangement of advanced lung cancer patients. Moreover she has been involved in a number of clinical trials sponsored by the farmaceutical industries, the Italian Medicines Agency (AIFA) as well as by Independent Research Programs.
Name and type of organisation providing education and training	Department of Oncology, University of Palermo Via del Vespro, 129 90127 Palermo Italy
Date	13/11/2008

Title of qualification awarded	Specialization Degree in Oncology (maximum marks cum laude)
Principal subjects/occupational skills covered	During her fellowship her research and clinical activities have been focused on diagnosis, staging, therapy and follow-up of the main solid tumors. Moreover she has been involved in a number of clinical trials sponsored by the farmaceutical industries, the Italian Medicines Agency (AIFA) as well as by Independent Research Programs.
Name and type of organisation providing education and training	Department of Oncology, University of Palermo Via del Vespro, 129 90127 Palermo Italy
Skills and competences	Her main fields of interest are the medical management of lung, head and neck, breast and colon cancers, the development of newer biological/targeted therapies, the design and conduct of clinical trials. She is member of the Italian Society of Medical Oncology (AIOM) since 2005, of the European Society of Medical Oncology (ESMO) since 2010, of the International Association for the Study of Lung Cancer (IASLC) since 2011. She has been chairman of one scientific meeting and invited speaker of 9 scientific meetings in Medical Oncology (7 in the last 3 years). 1) "Il carcinoma mammario, nuove prospettive terapeutiche" - Palermo, 15 novembre 2008 "Presentazione di un caso clinico" (Relatore) 2) "Attualità in tema di terapia medica del carcinoma colorettale" - Palermo, 4 dicembre 2009 "Presentazione di un caso clinico" (Relatore) 3) "La chemioterapia tra passato e presente: ritorno al futuro. Cipomo incontra AIOM Giovani" - Cava de' Tirreni (SA), 11-12 dicembre 2009 "Carcinoma polmonare non a piccole cellule in fase avanzata: relazione e discussione" (Relatore) 4) "ToGetErb2010: La nuova opzione terapeutica nel carcinoma mammario ErbB2+" - Palermo, 25 giugno 2009 "Presentazione di un caso clinico" (Relatore) 5) Convegno Nazionale AIOM Giovani Oncologi "2010 News in Oncology" – Brufa di Torgiano (PG), 9-10 luglio 2010 "Carcinoma polmonare: Terapia della fase avanzata" (Relatore) 6) Workshop multidisciplinare di aggiornamento "Riattivazione dell'Epatite B nel Paziente Immunocompromesso" – Palermo 27 Novembre 2010 "Presentazione di un caso clinico" (Relatore) 7) 2° Congresso Nazionale "Progressi nella terapia dei tumori solidi" – Palermo 1,2 Dicembre 2011 "Il paziente cirrotico compensato con malattia tumorale solida non HCC: trattare o non trattare? Proposta di una nuova linea guida" (Relatore) She is co-author of one chapter of an Oncology Textbook (2011), of 12 full scientific papers (5 in the last 3 years) and of 10 abstracts (8 in the last three years). She has been part of the writing committee of one clinical trial and co-investigator in a number (more than 25) of Industry and investigator's initiated GCP clinical trials.

LAST THREE YEARS BOOK CHAPTER

"Neoplasie a sede primitiva sconosciuta"

Palmeri S, Palmeri L, Vaglica M. In: "Oncologia clinica. Principi e pratica". Selecta Editrice, Pavia (2011). Ahead of Print.

LAST THREE YEARS FULL PAPERS

1. "Weekly docetaxel in the treatment of metastatic breast cancer"
Palmeri L, Vaglica M, Palmeri S. Therapeutics and Clinical Risk Management, 2008;4(5):1047–1059

2. "Role of loco-regional treatments for patients with breast cancer liver metastases"
Raimondi C, Danova M, Chatzileontiadou S, Palmeri L, Vercelli A, Palmeri S. Recenti Progressi in Medicina, 2009 Sep; 100(9): 424-33.

3. "Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer A randomized phase II SICOG trial"
Comella P, Chiuri VE, De Cataldis G, Filippelli G, Maiorino L, Vessia G, Cioffi R, Mancarella S, Putzu C, Greco E, Palmeri L, Costanzo R, Avallone A, Franco L. Lung Cancer 2010; 68 (1): 94-8

4. "Carcinosi peritoneale da neoplasia a sede primitiva sconosciuta con differenziazione neuroendocrina: sopravvivenza a lungo termine e ruolo degli analoghi della somatostatina"
Palmeri L, Rizzo S. Casi Clinici in Oncologia, 2010; volume 34 (accettato per pubblicazione)

5. "Should cirrhosis change our attitude towards treating non-hepatic cancer?"
Cabibbo G, Palmeri L, Palmeri S and Craxı A. Liv. Int. DOI: 10.1111/j.1478-3231.2011.0629.x (2011) (Epub ahead of print).

ABSTRACTS

1. "Alimta and gemcitabine in locally advanced or metastatic non-small cell lung cancer (NSCLC): the ANGEL trial (Southern Italy Cooperative Oncology Group phase II randomized trial 0506)"
Costanzo R, Chiuri VE, De Cataldis G, Filippelli G, Maiorino L, Vessia G, Cioffi R, Mancarella S, Putzu C, Greco E, Palmeri L, Avallone A, Comella P. 10th National Congress of Medical Oncology; 11-14 october 2008: Verona; abs C3 (oral communication)

2. "Serum HER-2/neu (s-HER2) levels evaluation in breast cancer(BC) patients (PTS)"
Palmeri L, Mangiameli A, Vaglica M, Frazzetta M, Vetri G, Di Noto L, Raimondi C, Accardo A, Bongiovanni A, Intrivici C, Palmeri S. 10th National Congress of Medical Oncology, 11-14 october 2008: Verona; abs M24 (poster)

3. "Final results of a phase II trial of a weekly (W) poly-chemotherapy (CT) with cisplatin (CDDP), epirubicin (EPI), fluorouracil (5FU), folinic acid (FA) and G-CSF for the treatment of locally advanced (LA) or metastatic (M) gastroesophageal (GE) and gastric (G) cancer (C) patients (pts)"

Palmeri L, Di Noto L, Vaglica M, Bongiovanni A, Iannitto E, Palmeri S. 2009 Gastrointestinal Cancers Symposium, 15-17 january 2009: San Francisco, CA; accepted for poster presentation.

4. "Evaluating the prognostic role of serum extracellular domain (ECD) of HER-2/neu (s-HER2) in patients (PTS) with metastatic (M) breast cancer (BC): results of an observational study"
Palmeri L, Vaglica M, Mangiameli A, Di Noto L, Bongiovanni A, Marchese A, Palmeri S. Ecco 15 – ESMO 34 Congress, Berlin 20-24 September 2009; Eur Jour Cancer Suppl, Vol 7 (2); p141; 1308P (accepted for poster presentation).

5. "Evaluating the prognostic role of serum extracellular domain (ECD) of HER-2/neu (S-HER2) in patients (PTS) with early (E) breast cancer (BC)".
L. Palmeri, M. Vaglica, A. Mangiameli, L. Di Noto, A. Bongiovanni, A. Marchese, and S. Palmeri. 11th National Congress of Medical Oncology, 10-13 october 2009: Milan; abs C22 (poster)

6. "Gastric cancer (GC) adjuvant (A) chemotherapy (CT): a literature based meta-analysis (MA) L. Palmeri, D. Matranga, M. Vaglica, A. Marchese, M. Frazzetta, G. Vetri, L. Di Noto, A. Bongiovanni, E. Liardo, S. Palmeri". Abstract Book of the 35th ESMO Congress Milan, Italy 8–12 October 2010; Ann Oncol (2010) 21 (suppl 8): viii225-viii249.

7. "Weekly docetaxel (Wdoc) for the treatment of metastatic (M) breast cancer (BC): a literature based meta-analysis (MA)".
L. Palmeri, et al. 12th National Congress of Medical Oncology, 6-8 November 2010: Rome (poster presentation).

8. " Non-Hepatic Cancer (NHC) and cirrhosis: to treat or not to treat? "
L. Palmeri et al. 13th National Congress of Medical Oncology, 5-7 November 2011: Bologna.

REVIEW

Weekly docetaxel in the treatment of metastatic breast cancer

Laura Palmeri
Marina Vaglica
Sergio Palmeri

Department of Oncology, University of Palermo, Palermo, Italy

Abstract: Breast cancer is the most frequent tumor among women worldwide and is the second cause of cancer-related mortality in the US. Metastatic breast cancer (MBC) accounts for less than 10% of newly diagnosed breast cancer patients and about 30% of early breast cancer patients will develop recurrent, advanced, or metastatic disease. It remains an incurable illness and the primary goal of its management is palliative. Several agents are active for the first-line treatment of MBC. The taxanes, paclitaxel and docetaxel, represent the standard of care for the treatment of these patients. Among the various schedules, docetaxel can be administered weekly, achieving similar efficacy results with lower toxicity compared with conventional schedules. Weekly docetaxel (25–40 mg/m^2) has been widely tested in several phase I and II studies both as a single agent and in multichemotherapy regimens, reaching overall response rates ranging from 26% and 86% or 20% and 73% with docetaxel alone or in combination, respectively, depending on doses, associations, and line of treatment. Overall, published data support the administration of weekly docetaxel for the treatment of MBC patients even if data from phase III randomized trials are still lacking.

Keywords: docetaxel, weekly, metastatic breast cancer, chemotherapy

Introduction

Breast cancer is the most frequent tumor among women worldwide and represents the second cause of cancer-related mortality in the US (SEER 2008).

Metastatic breast cancer (MBC) is uncommon as initial presentation, accounting for less than 10% of newly diagnosed breast cancer patients (SEER 2008). Despite optimization of treatment for early breast cancer, about 30% of women will develop recurrent, advanced, or metastatic disease. By 2003, 5-year relative survival exceeded 90% and 80% respectively for localized and regional breast cancer, while it did not reach 30% for MBC (Brenner et al 2007; Hayat et al 2007). The majority of breast cancer-related deaths are a result of complications from recurrent or metastatic disease.

MBC remains an incurable illness. The primary goal of its management is palliative and aims to improve quality of life, prolong disease-free survival (DFS) and possibly overall survival (OS). The main treatment modalities include endocrine therapy, cytotoxic chemotherapy and biological agents. The best option should be established considering multiple prognostic and predictive factors such as hormonal receptor status, HER-2 overexpression, growth rate, presence of visceral metastases, history of prior therapy and response.

Chemotherapy clearly provides tumor shrinkage and substantial clinical benefit in advanced breast cancer (Stockler et al 2000), so that it is accepted as standard treatment for hormone-resistant and rapidly progressive disease. On the other hand, no randomized trials comparing chemotherapy with supportive care only are available and such kinds of studies are unlikely to be considered ethical in the future.

Several agents are active for the first-line treatment of MBC, anthracyclines and taxanes being the most effective (Table 1).

Correspondence: Laura Palmeri
Division of Medical Oncology,
Department of Oncology, University of Palermo, Via Dell'Vespro 129- 90127 Palermo, Italy
Tel +39 091 6554167
Fax +39 6552 508
Email laura.palmeri@gmail.com

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Table 1 Most active drugs in first-line treatment of metastatic breast cancer and range of activity

	Objective response rate (%)
Adriamycin[1]	40–50
Epirubicin[1]	50–60
Paclitaxel[2]	29–42
Docetaxel[3]	47–65
Vinorelbine[4]	19–32
Gemcitabine[5]	25–46
Capecitabine[6,7]	20–30
Carboplatin[8]	20–25

[1]Findlay et al 1998; [2]Paridaens et al 2000; [3]Chan et al 1999; [4]Kerbrat et al 1998; [5]Blum et al 1999; [6]Blum et al 2001; [7]Tunekleau et al 2004; [8]Perez 2004.
Abbreviation: ORR, complete + partial response.

Anthracyclines provide an overall response rate (ORR) ranging from 35% to 50% as first-line single agents (Findlay et al 1998). Nowadays they are extensively used in the adjuvant setting so that many patients with recurrent disease may have already had a significant anthracycline exposure. Therefore taxane-based regimens are frequently considered for this subset of MBC patients.

Platinum compounds, alkylating agents, antimetabolites, and vinca-alkaloids might be also considered alone or in combination for the first-line treatment of MBC patients based on their single-agent activity (ORRs ranging from 18% to 52%) (Colozza et al 2007).

Several novel biological agents have recently started to be tested in such a setting of treatment: to date, only trastuzumab and bevacizumab, monoclonal antibodies against Her2/neu receptor and the vascular endothelial growth factor, respectively, have obtained regulatory agency approval, both in the US and in Europe. Trastuzumab is the standard therapy for HER-2 overexpressing tumors, both for early and advanced breast cancer patients, with response rates ranging from 50% to 70% with combination treatment (Slamon et al 2001; Burstein et al 2003; Marty et al 2005) and from 20% to 30% with monotherapy in the metastatic setting (Piccart-Gebhart et al 2005; Romond et al 2005). Bevacizumab has recently been approved for the first-line treatment of MBC patients, since its addiction to paclitaxel led to a significant prolongation of progression-free survival (median, 11.8 versus 5.9 months; hazard ratio [HR] for progression, 0.60; $p < 0.001$) and an increase in the objective response rate (36.9% versus 21.2%, $p < 0.001$) when the association was compared with single-agent paclitaxel (Miller et al 2007).

The results of the AVADO trial, comparing the efficacy of the association of bevacizumab (7.5 or 15 mg/kg) and docetaxel (100 mg/m²) with the standard 3-week docetaxel (100 mg/m²) as first-line treatment for MBC, were presented at the ASCO 2008 Annual Meeting (Miles et al 2008). Significant improvements in both progression-free survival (HR 0.79, CI 0.63–0.98, $p = 0.0318$ for bevacizumab at 7.5 mg/kg; HR 0.72, CI 0.57–0.90, $p = 0.0099$ for bevacizumab 15 mg/kg) and ORR (44.4% versus 55.2%, docetaxel alone versus the arm with bevacizumab 7.5 mg/kg, $p = 0.0295$; 44.4% versus 63.1%, docetaxel alone versus the arm with bevacizumab 15 mg/kg, $p = 0.0001$) have been found for the bevacizumab-containing arms compared with the docetaxel-alone arm.

The taxanes

The taxanes, paclitaxel and docetaxel, represent a milestone in the treatment of MBC. Although their synthesis began in the late 1970s, the clinical development for advanced breast cancer treatment burgeoned in the 1990s, when the first phase II trials documented their antitumor activity as single agents (Holmes et al 1991; Ringel et al 1991; D'Andrea et al 1997; Valero et al 1995).

Since then, data from prospective randomized phase III studies confirmed their activity and proved their efficacy, with single-agent paclitaxel and docetaxel providing similar OS rates compared with the previous gold standard anthracycline, doxorubicin (Chan et al 1999; Paridaens et al 2000; Sledge et al 2003). Moreover they demonstrated a significant activity in anthracycline-resistant patients and an acceptable toxicity profile (Ravdin et al 1995; Seidman et al 1995a, b; Nabholtz et al 1996, 1997).

In 2005, Ghersi et al published a comprehensive meta-analysis of all published and unpublished trials comparing regimens containing taxanes with those containing non-taxanes in the first-line and further lines of treatment in MBC, and found that taxanes combinations improved OS, time to progression (TTP), and ORR (Ghersi et al 2005). They also conducted a post-hoc sub-group analysis in order to investigate the treatment effect within the type of taxane. Data from the analysis of trials using paclitaxel showed no difference between the two arms for OS (HR 0.97; 95% CI = 0.87–1.07, $p = 0.54$), but when the taxane used was docetaxel there was a statistically significant difference in OS in favor of taxane-containing regimens (HR 0.88; 95% CI = 0.78–0.98, $p = 0.02$).

In previously untreated patients, single-agent docetaxel provides ORR of 40% to 68% (Cortes et al 1995; Valero 1997) while in anthracycline-resistant patients ORR is 53%–57% (Ravdin et al 1995; Valero et al 1995).

The first schedules of administration of docetaxel employed doses ranging from 75 to 100 mg/m² as a 1-hour intravenous infusion every three weeks. The 3-week schedule of docetaxel 100 mg/m², although extremely active, showed an important myelosuppression with more than 90% of cases experiencing grade (G) 3–4 neutropenia (Rivdin et al 1995; Valero et al 1995), with frequent non hematologic side effects including fatigue, alopecia, skin reactions, nails toxicity, fluid retention syndrome.

In pre-treated, elderly or poor performance status patients the 3-week dose of 100 mg/m² must be frequently reduced to 75 mg/m² (O'Brien et al 1999; Salminen et al 1999).

Furthermore, such a toxicity profile made it difficult to combine docetaxel with other active chemotherapeutic agents, limited its use in unfit patients and affected dose-intensity.

In order to go beyond these difficulties new treatment regimens of docetaxel have been proposed and the weekly administration has been widely experimented during the last years.

In fact, the weekly schedule provides a remarkable reduction of toxicities, especially hematologic, while maintaining the high activity of docetaxel. An additional advantage for the weekly schedule might be an equivalent dose intensity of treatment compared with the three-week administration of docetaxel at the dose of 100 mg/m2, so allowing a prolonged exposure to the drug of the different tumor cell clones, preventing the emergence of resistant clones.

Docetaxel is also a potent and potentially specific inhibitor of endothelial cell migration in vitro and angiogenesis in vitro and in vivo. The antiangiogenic activity of docetaxel in vivo was assessed by Hotchkiss et al In this assay, the angiogenic response to fibroblast growth factor 2 was inhibited in vivo by docetaxel with an ID50 of 5.4 mg/kg when injected twice weekly over a 14-day period and angiogenesis was completely blocked in mice that received 10 mg/kg docetaxel (Hotchkiss et al 2002).

Our review focus on the role of the weekly schedule of administration of docetaxel as single agent therapy and as a part of combination regimens for the treatment of MBC patients.

Weekly single-agent docetaxel: phase I studies

Many phase I trials of weekly docetaxel, either as single agent or in combination, have been carried out and published (Table 2).

Table 2 Selected phase I trials on weekly docetaxel

Author and year of publication	N. of pts (BC pts)	Regimen	MTD – DLT
Weekly single-agent docetaxel			
Tomiak et al 1994	21 (6)	Doc 20–35 mg/m² d 1,8 o 21	35 mg/m² – neutropenia
Hainsworth et al 1996	28 (7)	Doc 20–32 mg/m² ow × 6w (2 w rest)	32 mg/m² – fatigue –asthenia
Luck et al 1997	18 (all)	Doc 20–30 mg/m² ow	MTD not reached – no DLT
Loffler et al 1998	31 (all)	Doc 20–45 mg/m² ow × 6w (2 w rest)	40–45 mg/m² – leukopenia
Brizzolis et al 1999	26 (1)	Doc 25–30 mg/m² ow	30 mg/m² – leukopenia
Kourousis et al 2000	26 (19)	Doc 20–45 mg/m² ow × 2w (1 w rest)	42 mg/m² – neutropenia
Nitsticò et al 2005	28 (all)	Doc 20–40 mg/m² ow × 24 w	35 mg/m² – asthenia
Weekly docetaxel in combination with chemotherapeutic agents			
Frasci et al 2000	24 (all)	Doc 20–45 mg/m² d 1,8 o 2w with Gem 1000 mg/m² d 1,8 o 2w or VNR 25 mg/m² d 1,8 o 2w	30 mg/m² – neutropenia
Ito et al 2001	25	Doc 25–30 mg/m² ow × 6w with Dox 15–20 mg/m² ow × 6w	30 mg/m² – neutropenia
Wenzel et al 2002	12 (all)	Doc 25–40 mg/m² ow × 6w (1w rest) with Epidox 25–25 mg/m² ow × 6w (1w rest)	40 mg/m² – neutropenia
Brugnatelli 2002	18 (all)	Doc 20–40 mg/m² ow × 2w (1w rest) with Gem 800 mg/m² ow × 2w (1w rest)	40 mg/m² – asthenia – stomatitis – leukopenia
Ibrahim et al 2007	11 (all)	Doc 20–25 mg/m² ow × 2w (1w rest) with Dox 20–40 mg/m² + Cyc 500 mg/m² ow × 2w (1w rest)	20 mg/m2 – febrile neutropenia

Abbreviations: Pts, patients; BC, breast cancer; MTD, maximum tolerated dose; DLT, dose limiting toxicity; w, week; Doc, docetaxel; Gem, gemcitabine; VNR, vinorelbine; Epidox, epidoxorubicin; Dox, doxorubicin; Cyc, cyclophosphamide.

In 1994, Tomiak et al evaluated first the weekly administration of docetaxel in 32 patients with advanced refractory cancer, at doses ranging from 20 to 110 mg/m² on days 1 and 8 of a 21-day cycle (Tomiak et al 1994).

The first phase I study, investigating a 6-week consecutive administration of docetaxel with a 2-week rest period, was initiated in 1996 by Hainsworth et al to define the optimum dose of weekly docetaxel. Thirty-eight patients (7 with refractory breast cancer), included in sequential cohorts, received escalating doses of docetaxel (20–52 mg/m²/week) until dose-limiting toxicity (DLT) occurred. They reported fatigue and asthenia as the DLTs for this regimen. No patient showed G4 leucopenia at any dose level. In this study the maximum tolerated dose (MTD) was 43 mg/m²/week (corresponding to a dose-intensity of 126 mg/m² every 3 weeks) (Hainsworth et al 1998).

In 1997, Luck et al performed a phase I trial on 18 pre-treated advanced breast cancer patients. Dose levels between 30 and 50 mg/m² were used weekly: no DLT occurred and the MTD was not reached (Luck et al 1997).

Loeffler et al conducted a phase I/II trial on 31 patients with advanced breast cancer. Weekly docetaxel (30–45 mg/m²/week) was administered for 6 consecutive weeks followed by a 2-week rest period. An ORR of 50% was reported. The recommended dose for phase II trials was 40 mg/m²/week (Loeffler et al 1998).

In another subsequent phase I study, Briasoulis et al treated 36 cancer patients with weekly docetaxel at doses ranging from 25 to 50 mg/m²/week. They found myelosuppression and diarrhea being the DLTs and suggested the dose of 40 mg/m²/week for further investigations (Briasoulis et al 1999).

In the study conducted by Kourossis et al in 26 advanced solid tumors patients (19 with MBC), the authors reported an ORR of 39% and recommended a dose of 40 mg/m²/week (Kouroussis et al 2000).

Nistiò et al conducted a phase I/II trial on 28 patients with pretreated MBC. Weekly docetaxel was administered weekly at a dose range of 30–40 mg/m²/week for 24 consecutive weeks (Nistico et al 2005). The suggested dose for phase II trials was 35 mg/m²/week. Two out of 28 evaluable patients (7.1%) showed complete response (CR), 8 partial response (PR) (28.6%), and 8 stable disease (SD) (28.6%). Median TTP and OS were 5 and 15 months, respectively. Only one G3 neutropenia occurred, while severe asthenia was the main reason for treatment stop (10 patients, 35.5%) before the planned 24 weeks.

Overall, these tested weekly dosages are equivalent to a dose range of 105–120 mg/m² every 3 weeks.

Weekly docetaxel in combination regimens: phase I studies

The favorable results arising from single-agent use prompted its combination with other active drugs (Table 2).

In 2000, Frasci et al studied the association between escalating doses of docetaxel (starting from 30 mg/m²) and either gemcitabine 1000 mg/m² or vinorelbine 25 mg/m², all on days 1 and 8 every three weeks for the treatment of 34 anthracyclines pre-treated MBC patients; 24 out of 34 had received weekly dose-dense paclitaxel as second-line treatment (Frasci et al 2000). Docetaxel at the dose of 40 and 35 mg/m² proved to be safe when combined with gemcitabine and vinorelbine respectively. An ORR of 15% was observed (95% CI: 5%–31%) and only 1 of 24 paclitaxel pretreated patients responded to treatment.

Twenty-five patients with advanced breast cancer were treated by Ito et al with an intravenous bolus of doxorubicin (15–20 mg/m²), immediately followed by a 1-h infusion of docetaxel (25–30 mg/m²), every week for 6 weeks (Ito et al 2001). MTD was 20 mg/m² and 30 mg/m² for doxorubicin and docetaxel, respectively. Overall, modest neutropenia was reported with no febrile episodes with doxorubicin 15 or 20 mg/m² and docetaxel 25 mg/m² or lower. Reported G3 non-hematologic toxicities included asthenia in 4% of patients, anorexia in 8%, and vomiting in 8%. The ORR was 56% (14/25 with partial response). The recommended dose for further investigation was 20 mg/m² of doxorubicin and 25 mg/m² of docetaxel.

Weekly epidoxorubicin (25–35 mg/m²) and docetaxel (25–40 mg/m²) given once a week for 6 weeks followed by 1-week rest were evaluated for the preoperative and palliative treatment of patients with breast cancer by Wenzel et al DLT was neutropenic fever, occurring with 35 mg/m² of epidoxorubicin and 40 mg/m² of docetaxel. Epidoxorubicin 30 mg/m² and docetaxel 35 mg/m² were suggested for further evaluations (Wenzel et al 2002).

In order to determine the maximum tolerable dose of docetaxel in association with gemcitabine, both given on a weekly schedule, Brugnatelli et al designed a phase I study using three escalating doses of docetaxel (30, 35, and 40 mg/ m²) followed by a fixed dose of gemcitabine, 800 mg/m², on days 1, 8, and 15 of a 28-day cycle (Brugnatelli et al 2002). Asthenia, stomatitis, and leukopenia were the main DLTs. An objective response rate of 58% was found and the dose of 35 mg/m² was proposed for further phase II evaluation.

In a recent phase I trial, 11 MBC patients were enrolled in an open, single-arm phase I escalation trial in 3–6 patients/cohort (Ibrahim et al 2007). The treatment schedule was: docetaxel 20 mg/m² (or 25, depending on dose level assignment) on day 1, 8, 15 in association with doxorubicin 40 or 50 mg/m² and cyclophosphamide 500 mg/m² on day 1, every 4 weeks. Five patients were allocated to dose level 20/50 (docetaxel/doxorubicin) and 6 to dose level 20/40. MTD was defined at 20 mg/m² for docetaxel in combination with doxorubicin 40 mg/m² and cyclophosphamide 500 mg/m², due to DLT febrile neutropenia.

Weekly single-agent docetaxel: phase II studies

Several phase II trials have evaluated the weekly administration of single-agent docetaxel in MBC patients (Table 3).

In 2000 Burstein et al published the results of a study of weekly docetaxel administered at the dose of 40 mg/m²/week to 29 patients (Burstein et al 2000). The authors reported an ORR of 41% (all PRs), with similar results for both first- and second-line treatment (21% of second-line patients). Grade 3 toxicities, most commonly neutropenia and fatigue, were reported in 28% of patients, whereas fatigue, fluid retention, and eye tearing/conjunctivitis were found to be related to cumulative dose. Dose reductions were required for 8 patients, mostly due to fatigue.

Jackisch et al (2000) presented, in abstract form, the preliminary results of a multicentric phase II study designed to determine response rate and toxicity of weekly docetaxel 35–40 mg/m² in 60 MBC patients (second line 1.9%, third line 98.1%). Overall 24 patients (42.9%) were pretreated with anthracyclines for MBC. The reported ORR was 33.4% including 4/60 CR (6.7%) and 16/60 PR (26.7%). Regarding toxicity, 23/652 (3.5%) cycles were associated with G3 neutropenia, and 2/652 (0.3%) cycles with G3/4 thrombocytopenia. Non-hematologic G3 side effects were: 14.3% alopecia, 1.2% skin disorder, 0.8% neurotoxicity, 0.8% mucositis, 0.8% nausea/vomiting, 1% fluid retention, with no G4 non-hematologic toxicities. The authors found this schedule safe and feasible, achieving good response rates in heavily pretreated MBC patients.

Stemmler et al (2001) conducted a phase II trial in 35 previously treated MBC patients. Docetaxel 35 mg/m²/week for 6 weeks followed by 2 weeks of rest was administered with an ORR of 34%. A median survival of 11 months and a progression-free survival of 2.6 months were reported. G3 neutropenia was observed in 3 patients.

Hainsworth et al (2001) tested a weekly schedule of docetaxel 36 mg/m²/week in 41 elderly (median age 74 years) or poor performance status MBC patients (75% as first-line treatment). In this cohort 36% had an ORR, median TTP was 7 months, and median survival was 13 months. Fatigue was the most common G3/4 non-hematologic toxicity.

In another phase II study, 37 MBC patients (previously treated in 92% of cases) received docetaxel at 40 mg/m²/week for 3 consecutive weeks with 1-week rest (Aihara et al 2002).

Table 3 Recent selected phase II trials on weekly docetaxel

Author and year of publication	N. of pts (line)	Regimen	ORR
Weekly single-agent docetaxel			
Burstein et al 2000	29 (21% 2nd line)	40 mg/m² ow	41%
Jackisch et al 2000	60 (92.2% 2nd or > line)	35–40 mg/m² ow	33.4%
Stemmler et al 2001	35 (all 2nd or > line)	35 mg/m² ow × 6w (2 w rest)	34%
Aihara et al 2002	37 (all 2nd or > line)	40 mg/m² ow × 3w (1 w rest)	36% (32 evaluable pts)
Hainsworth et al 2001	41 (25% 2nd or > line)	36 mg/m² ow	36%
Ramos et al 2002	35 (all Anthra resistant)	36–40 mg/m² ow × 6w (2 w rest)	34%
D'Hondt et al 2004	47 (79% 2nd or > line)	36 mg/m² ow × 6w (1 w rest)	30% (27 evaluable pts)
Stemmler et al 2005	54 (all 1st line)	35 mg/m² ow × 6w (2 w rest)	48.1%
Ford et al 2004	42 (62% 2nd line)	25mg/m² ow × 6w (2 w rest)	26%
Weekly versus 3-week single-agent docetaxel			
Sedlir et al 2002	30 (overall 40% 2nd line)	25 mg/m² ow × 6w (2w rest) versus 100 mg/m² d 1 o 21	86.7% versus 73.2%
Tabernero et al 2004	41 (17% 2nd line) 42 (20% 2nd line)	40 mg/m2 ow versus 100 mg/m² d 1 o 21	34% versus 22%

Abbreviations: Pts, patients; ORR, complete + partial response; w, week; Anthra, anthracycline.

An ORR of 38% (14 partial responses) was found, with a TTP of 5 months and an OS of 12 months. Regarding toxicity, 19% of patients experienced G3/4 neutropenia with no case of febrile neutropenia. Although degree of toxicity was not severe in many cases, it was the most common cause for delay of the treatment and dose reduction. None of the patients showed G3/4 non-hematologic toxicity. Fatigue and asthenia, generally mild, were observed in 35% of patients and generally mild. Gastrointestinal side effects and skin/nails changes were relatively frequent (38% and 39% respectively).

In 2003, Ramos et al (2003) reported on 35 MBC patients resistant to prior anthracycline chemotherapy treated with docetaxel 40 mg/m² for 6 consecutive weeks followed by a 2-week rest, then reduced to 36 mg/m² due to non-hematologic toxicity (28% G3/4 asthenia). ORR was 34% (2 CR and 10 PR). After a median follow-up of 11.4 months, median TTP was 8.4 months, while median OS was 13.6 months. The most severe hematologic toxicity (17% of patients) was neutropenia whereas asthenia, nail, ocular, and skin disorders were the main non-hematologic toxicities. One treatment-related death occurred during further follow-up (pulmonary fibrosis).

In order to evaluate the safety and efficacy of weekly docetaxel in frail and/or elderly patients, who were ineligible for the standard 3-weekly docetaxel (100 mg/m²) regimen, D'Hondt et al (2004) performed a phase II study for the treatment of 47 MBC patients. Docetaxel was given at the dose of 36 mg/m² weekly for 6 weeks followed by a 1-week rest. There was a median of 2 prior chemotherapy regimens and more than 60% had a WHO performance score at baseline of 2–3. Noteworthy, the ORR, in 37 evaluable patients, was 30%. Six patients experienced G3 and 4 patients G4 neutropenia. Of these 10 patients, 4 developed neutropenic fever. Neurotoxicity was mild and G3 parasthesia occurred in 1 patient. The authors conclude that weekly docetaxel (36 mg/m²) is active, safe and overall well tolerated also in heavily pretreated frail/elderly patients.

In a multicenter phase II study published in 2005, Stemmler et al (2005) prospectively analyzed the activity of weekly docetaxel in 54 first-line MBC patients. Docetaxel was given at a dose of 35 mg/m² weekly for 6 weeks followed by 2 weeks of rest with an ORR of 48.1%. Median survival was 15.8 months, while median TTP was 5.9 months. G3 neutropenia was reported in 3.7% of patients with no case of febrile neutropenia. Among the non hematologic toxicities G3/4 asthenia was observed in 5.6% and nausea/vomiting in 3.7% of cases. The toxicity profile did not differ significantly between younger (<65 years) and elderly patients (>65 years), except for fluid retention syndrome and neurotoxicity that showed an increased incidence in the younger patients.

In 2006 Ford et al (2006) evaluated docetaxel 35 mg/m² weekly for 6 weeks followed by a 2-week rest, in 42 anthracycline-pretreated MBC patients (second-line treatment in 62% of patients). They reported an ORR of 26% (11 partial responses); 5 of these responding patients had relapsed <12 months after the end of previous anthracycline-based chemotherapy. Myelosuppression was rare, with only 2 patients (5%) experiencing G3 neutropenia (no G4 neutropenia). Non-hematologic G3 toxicities were: fatigue 17%, neuropathy 0%, hyperlacrimation 5%, stomatitis 7%, diarrhoea 14%, and cutaneous toxicity 19% (limb/palmar-plantar erythematous reactions, or fixed-plaque erythrodysaesthesia). The authors do not recommend this weekly regimen due to the significant non-hematological toxicities associated with the treatment.

Sedky et al (2002) conducted a randomized phase II trial, presented in an abstract form, to compare weekly docetaxel at a dose of 35 mg/m² for 6 weeks followed by 2 weeks rest, with docetaxel at a dose of 100 mg/m² every 3 weeks in 30 MBC patients. There was no statistical difference between the weekly and the every 3-week treatment arms for ORR (86.7% versus 73.3% respectively), neutropenia being less with the weekly regimen.

A randomized phase II study (Tabernero et al 2004) was performed to compare weekly versus every 3-week docetaxel at a dose of 40 mg/m² and 100 mg/m², respectively, in 83 MBC patients. ORR was 34% in the weekly and 33% in the every-3-week arm; median TTP was 5.7 versus 5.3 months, while the median time to treatment failure was 4.1 and 4.9 months, respectively. In terms of tolerability, the incidence of all G3/4 adverse events was higher in the every-3-week arm. In particular G3/4 neutropenia, neutropenic fever, stomatitis, and neurosensory toxicity had a lower incidence in the weekly docetaxel arm.

Weekly docetaxel in combination regimens: phase II studies

Since encouraging results came from phase II studies on weekly single-agent docetaxel, it has been investigated in combination with either chemotherapeutic or biological agents (Table 4).

The combination of weekly docetaxel and vinorelbine was investigated in 57 MBC patients (first line in 42 cases) (Kornek et al 2001). Therapy consisted of vinorelbine 30 mg/m² on days 1 and 15 and docetaxel 30 mg/m² on

Table 4 Recent selected phase II trials on weekly docetaxel in combination regimens

Author and year of publication	N. of pts (line)	Regimen	ORR
Kornek et al 2001	57 (26% 2nd line)	VNR 20 mg/m² d1,15 q 4w with Doc 30 mg/m² d1,8,15 q 4w	64% as 1st line 52% as 2nd line
Palmeri et al 2005	58 (1st line)	Doc 35 mg/ m² d1,8,15 q 4w with Gem 800 mg/ m2 d1,8,15 q 4w	64% (56 pts evaluable)
Mrozek et al 2006	29	Doc 30 mg/m² ow × 3w (1 w rest) with Cap 600 mg/m2 bid d1-21 q 4w	44%
Esteva et al 2002	20 (19% 2nd line)	Doc 25 mg/m² ow × 3w (1 w rest) with T 2 mg/kg ow × 3w (1w rest)	62%
Raab et al 2002	12 (1st line) 12	Doc 25 mg/m² ow × 6w (2 w rest) + T 2 mg/kg/ow versus Doc 100 mg/m² d1 q21 + T 2 mg/kg/ow	Overall 62%
Tedesco et al 2004	26 (15% 2nd line)	Doc 25 mg/m² ow × 6w with T 2 mg/kg ow × 3w	50%
Rasf et al 2004	21 + 14 + 17 (Her2 +)	Doc 22 mg/m² d1,8,15 q 4w Doc 40 mg/m² d1,8,15 q 4w + T 2 mg/kg d8,15 q 4w (T only for 17 additional Her2 + pts)	21% 59%
Ramaswamy et al 2006	27 (22% 2nd line)	Doc 25 mg/m² d1,8,15 q 4w with B 10 mg/kg d1,15 q 4w	52%
Ghosn et al 2006	62 (1st line)	NAVCAF 6 cycles versus NAVCAF 4 cycles + Doc ow x 12 wk	(Overall 65% after first 4 cycle of NAVCAF) Not yet available
Peacock et al 2006	61 (1st line)	Doc 30 mg/m² d1,8 q 3w with VNR 25mg/m² d1,8 q3w with T 2 mg/kg ow	67%
Rossi et al 2006	20 + 28 (All 1st line)	Doc 30 mg/m² ow × 3w (1 w rest) or P 50 mg /m² ow × 3w (1 w rest) with NPL-Anthra 25 mg/m² ow x 3w (1 w rest)	Overall 72%
Waterhouse et al 2006	22 (55% 1st line)	Doc 30 mg /m² ow × 3w (1w rest) with Imatinib 600 mg daily	20% (18 evaluable pts)

Abbreviations: Pts, patients; ORR, complete + partial response; w, week; VNR, vinorelbine; Doc, docetaxel; G, gemcitabine; Cap, capecitabine; T, trastuzumab; P, paclitaxel; B, bevacizumab; NAVCAF, VNR 25 mg/m² d1,8 + Cap 825 mg/m² bid D1–14 q3w; NPL-Anthra, non-pegylated liposomal anthracycline.

days 1, 8, and 15 every 28 days. Depending on the absolute neutrophil count on the day of scheduled administration, a 5-day course of G-CSF 5 μg/kg/d was given. ORR was 64.3% in patients receiving docetaxel plus vinorelbine as first-line chemotherapy, including 8 CR (19%) and 19 PR (45.3%); 11 patients (26.2%) had disease stabilization and 4 (9.5%) experienced disease progression. As second-line treatment, this regimen resulted in 8 (53.3%) objective responses. Median TTP was 12 months in the first-line and 9.8 months in the second-line setting. After a median follow-up of 18 months, 38 patients (65%) were still alive (with metastatic disease). Regarding hematologic side effects, G3 or G4 neutropenia occurred in 18 patients (32%) and was complicated by septicemia in 4 cases; G3 or G4 thrombocytopenia was reported in 2 patients (4%) and G3 anemia was seen in 1 patient (2%). Severe (G3) non-hematologic toxicities, except for alopecia, were rarely observed and included nausea/vomiting in 2 patients (4%) and stomatitis, peripheral neuropathy, and skin toxicity, each in 1 case.

A multicenter phase II study focused on weekly docetaxel 35 mg/m² in combination with gemcitabine 800 mg/m² on days 1, 8, 15 of an every-28-days cycle as first-line treatment in 58 MBC patients (Palmeri et al 2005). At least 1 visceral site of metastasis was present in 45 (77.6%) patients. In the 56 assessable patients, ORR was 64.3% with 9 patients (16.1%) achieving a CR, 27 (48.2%) a PR, and 12 (21.4%) patients SD.

Median survival was 22.10 months, with 43 (74.1%) patients still alive at the cut-off date of 36 months. Noteworthy, TTP was 13.6 months. Median time to treatment failure was 8.6 months (95% CI: 4.79–12.41). At the time of cut off, 24 patients had experienced progressive disease (PD). Median duration of response in patients with SD was 19.27 months. Furthermore, median survival of patients who achieved PR was 29.30 months. G3/4 neutropenia occurred in 8 patients (14%). Regarding non-hematologic toxicity, G3 alopecia was experienced by 5 patients (9%). No case of fluid retention syndrome was seen.

The activity and tolerability of weekly docetaxel (30 mg/m² on days 1, 8, and 15) and capecitabine (800 mg/m² twice daily on days 1–21) repeated every 28 days was evaluated in 39 patients with MBC (Mrozek et al 2006). ORR was 44%, with a median duration of response of 9.1 months. Median TTP was 5.5 months. G3 non-hematologic toxicities were asthenia (18%), diarrhea (18%), nausea/vomiting (13%), stomatitis (13%), and hand-foot syndrome (10%); among the hematological toxicities, 13% of patients experienced neutropenia. There were 2 G4 toxicities (febrile neutropenia and pulmonary embolism).

In HER-2 overexpressing MBC patients, weekly docetaxel has been largely evaluated in combination with trastuzumab.

A phase II study was performed in 30 MBC women (19% in second line) with a median age of 45 years (Esteva et al 2002). The authors evaluated docetaxel 35 mg/m²/week and trastuzumab (loading dose of 4 mg/kg followed by 2 mg/kg) weekly for 3 weeks followed by 1-week rest. They reported an ORR of 63% (RP in 19 patients); according to the HER-2 extracellular domain level, 21 patients with baseline levels >14.9 ng/ml had an ORR of 76% while those with normal levels had an ORR of 33%. The median TTP was 9 months. The main G3/4 toxicities were granulocytopenia (26%), fatigue (20%), and diarrhea (6%).

A phase II randomized study compared every-3-week docetaxel and trastuzumab with a weekly regimen (docetaxel 35 mg/m² for 6 weeks with 2-week rest) as first-line treatment in 25 patients with anthracycline-pretreated, HER-2 overexpressing MBC (Raab et al 2002). Overall the ORR was 63% and median TTP was 8.3 months. G3/4 hematologic side effects were frequent in the every-3-week group, including leukopenia, neutropenia (92%), and febrile neutropenia (23%).

A phase II study evaluated the combination of weekly docetaxel (35 mg/m²/week for 6 weeks) and trastuzumab (4 mg/kg load; 2 mg/kg/week) as first- or second-line (15%) therapy in 26 women with HER-2-overexpressing MBC (Tedesco et al 2004). ORR was 50%. With regard to HER-2 3+ patients, the reported ORR was 63%, compared with a 14% response rate for HER-2 2+ patients ($p = 0.07$). Patients with FISH-positive tumors experienced an ORR of 64%. Median time to progression was 12.4 months for the entire group and median survival was 22.1 months. G4 toxicities occurred in 4 patients.

The combination of weekly docetaxel and trastuzumab was also evaluated in 52 MBC patients (Raff et al 2004). They received docetaxel given on 2 different schedules: 21 patients in group 1A, 33 mg/m² weekly; 14 in group 1B, 40 mg/m² weekly for 3 weeks with 1-week rest. Patients with HER-2/neu overexpressing disease also received trastuzumab 4 mg/kg on day 1, then 2 mg/kg on days 8 and 15 of each 28-day cycle (group 2). Previous every-3-week taxane therapy had been used for metastatic disease in 19 of 35 patients (54%) in group 1A/B and in 2 of 17 patients (12%) in group 2. ORR (PR) was 21% in patients treated with docetaxel alone, including 3 of 19 taxane-pretreated patients (16%) and 4 of 16 taxane-naive patients (25%). Partial response occurred in 59% of cases treated with docetaxel/trastuzumab. Median TTP was 4.5 months in the docetaxel group and 8.5 months in the docetaxel/trastuzumab group. The main G3/4 toxicities (>10% of patients) observed were neutropenia (21%), pulmonary toxicity (12%), and hyperglycemia (10%).

Finally, a pilot study of preoperative weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg/week), in association with weekly epidoxorubicin 30 mg/m²/week and docetaxel 35 mg/m²/week for 6 weeks with 1 week was conducted on 14 consecutive patients (Wenzel et al 2004). Overall the regimen was well tolerated, with major responses observed in 12 out of 14 patients (86%) leading to breast-conserving surgery in 11 of 14 patients (79%).

The safety and efficacy of bevacizumab and weekly docetaxel as first or second line treatment was evaluated in 27 MBC patients (Ramaswamy et al 2006). ORR was 52% and the median progression-free survival was 7.5 months. The most common G4 toxicities were: pulmonary embolus (7%), febrile neutropenia (4%), and infection (4%).

Four recent studies evaluating weekly docetaxel in combination with both chemotherapeutic and/or biological agents, for the treatment of MBC were presented at the 2008 ASCO annual meeting, demonstrating the growing interest for such a feasible and active schedule.

On the basis of a proven prolonged TTP and OS of the sequential use of vinorelbine (25 mg/m² d1,8) and capecitabine (825 mg/m² bid d1–14) (NAVCAP)

every 3 weeks for 4 cycles followed by 12 consecutive weeks of docetaxel (25 mg/m²/w) in the first-line treatment of MBC, Ghosn et al (2008b) designed and conducted a further phase II randomized trial. Preliminary data from this study have been also presented in abstract form (Ghosn et al 2008a). Sixty-three first-line HER-2/neu negative MBC patients were enrolled and 44 have been randomized after the first 4 cycles of NAVCAP to receive either 4 more cycles of NAVCAP (25 patients) or 12 weekly docetaxel (19 patients). Overall, after the first 4 cycles of NAVCAP an ORR of 65% with 17% of CR was registered (SD 21%). Nineteen and 12 patients had completed the treatment plan at the time writing. With regard to tolerability, patients treated with NAVCAP experienced G3 neutropenia in 8% of cases, G3/4 anemia in 6%, and 1 patient had G3 hand-foot syndrome; in patients treated with docetaxel, 11% had G4 liver enzymes elevation and 1 patient had G4 creatinine elevation. No long-term follow-up data were available in order to determine whether maintenance docetaxel will have an added value versus maintenance NAVCAP.

The feasibility and safety of a 3-drug combination of trastuzumab, docetaxel, and vinorelbine as first-line therapy was investigated in 61 HER-2 positive MBC. The schedule included docetaxel 30 mg/m² and vinorelbine 25 mg/m² on days 1 and 8 of a 3-week cycle in association with weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg/week) (Peacock et al 2008). The reported ORR was 67% (CR 26%, PR 41%). After a median follow-up of 58 months, median progression-free survival was 11.3 months and median OS was 39.1 months. The most common hematologic toxicity was neutropenia (G4 in 72%); 8 patients (13%) were hospitalized for febrile neutropenia. Other G3/4 toxicities included fatigue (12%), hyperglycemia (7%), and myalgias (7%).

Rosati et al (2008) presented results of their phase I/II trial in first-line MBC patients (adjuvant anthracyclines and taxanes were allowed). The dose-finding study examined the safety and activity of weekly combination (d 1, 8, 15 q4w) of paclitaxel (n = 28 patients) or docetaxel (n = 20 patients) with non-pegylated liposomal anthracycline. DLT was 50 mg/m² and 30 mg/m² for paclitaxel and docetaxel respectively, combined with 25 mg/m² of non-pegylated liposomal anthracycline. A phase II trial followed and 48 patients were enrolled. The reported ORR was 73% (12.5% CR and 60.41% PR), with a clinical benefit of 85.41%. Median TTP was 10.68 months. No survival differences were recorded between paclitaxel and docetaxel groups. G3/4 toxicities included neutropenia (68.75%) and alopecia (60.41%). Overall the following non-hematologic toxicities were significantly higher for docetaxel than paclitaxel: mucositis 12.53% versus 8.3%, onycholysis 22.91% versus 10.41%, and peripheral sensory neuropathy 25% versus 14.58%. The authors concluded that weekly administration of taxane and non-pegylated liposomal anthracycline is well tolerated and clinical benefit data encourage a phase III study design.

The association between weekly docetaxel and imatinib mesilate has been studied in a phase II study designed to investigate whether adding imatinib could ameliorate docetaxel performance in first- or second-line MBC patients (Waterhouse et al 2008).

Docetaxel was given weekly 30 mg/m² days 1, 8, and 15 q28 for 6 cycles with daily oral imatinib 600 mg until PD. To date, only data on toxicity of 33 patients have been published (55% first line and 42% second line; 13 patients had prior taxanes). Overall, hematologic side effects were mild with G3/4 neutropenia 12% (1 febrile neutropenia) and anemia 9%. On the other hand, G3/4 non-hematologic, especially gastrointestinal, toxicity prompted imatinib dose modification to 400 mg after the first 14 patients. No improvement in gastrointestinal toxicity has been recorded despite dose reduction: G3/4 diarrhea 21%, nausea 18%, and vomiting 12%, with 9 patients requiring treatment–related hospitalizations (gastrointestinal toxicity 4, febrile neutropenia 1, pleural effusion 2, and pneumonia 2). Only 5 patients went on to maintenance imatinib with a median of 6 cycles. Four out of 18 evaluable patients had PR, 8 patients SD, while 6 patients progressed. Median TTP and OS were 3 and 10 months, respectively. Although presented data are preliminary, no therapeutic advantage resulted from adding imatinib to weekly docetaxel in MBC.

Weekly single-agent docetaxel: phase III studies

To date only 3 phase III randomized trials have been performed to investigate the efficacy of weekly docetaxel (Table 5).

In 2004, Meier et al reported, in abstract form, a planned interim analysis of a phase III trial comparing weekly vinorelbine versus weekly docetaxel for metastatic breast cancer failing anthracyclines (Meier et al 2004). Crossing-over was allowed on disease progression. They analyzed data from 120 of 240 patients accrued from November 1998 until July 2003 and randomized to receive either vinorelbine 30 mg/m² or docetaxel 35 mg/m² weekly for 6 consecutive weeks of a 8-week cycle. At the time of the analysis 112 patients were evaluable. TTP was the main endpoint of the study: 81 days

Table 5 Phase III trials

Author and year of publication	N. of pts	Regimen	TTP (months)	PFS	OS
Meier et al 2004	55	Doc 35 mg/m² qw × 6w (2w rest) versus VNR 30 mg/m² qw × 6w (2w rest)	2.7 versus 3.4	Not reported	9.4 months versus 8.42 months
	57		(p = 0.1178)		(p = 0.1895)
Burstein et al 2007	40	Doc 35 mg/m² × 6w/P 80 mg/m² × 8w + T 2mg/kg qw versus VNR mg/m² + T 2 mg/kg qw	6 versus 8.5	Not reported	Not reported
	41		(p = 0.09)		
Rivera et al 2008	59	Doc 75 mg/m² d 1 o 21 versus Doc 35 mg/m² d 1,8,15 o 22	Not reported	5.7 months versus 5.5 (p = 0.46)	18.2 months versus 18.4 (p = 0.34).
	59				

Abbreviations: Pts, patients; BC, breast cancer; TTP, time to progression; OS, overall survival; w, week; Doc, docetaxel; VNR, vinorelbine.

(CI: 67–99) versus 103 days (CI: 98–119) were registered for vinorelbine versus docetaxel (p = 0.1178). OS was 253 (CI: 173–331) versus 288 days (CI: 231–424) for initial vinorelbine versus docetaxel (p = 0.1895). Significantly more patients receiving vinorelbine (42%) had disease progression as best response than patients receiving docetaxel (18%) (p = 0.00751). Moreover, vinorelbine resulted in more treatment delays (76% versus 46%), more leukopenia (61% versus 10%) and G3/4 neutropenia (43% versus 7%), but less mucositis/stomatitis (1% versus 8%) (all p < 0.05). The authors found weekly docetaxel more efficient at response and less toxic than weekly vinorelbine, but more mature data are needed in order to clarify the benefit. To our knowledge, no definitive data are available to date.

Burstein et al studied the combination of trastuzumab with either vinorelbine or a taxane as first-line treatment in 81 out of the 250 originally planned HER-2 positive MBC patients (the study was terminated early because of poor accrual) (Burstein et al 2007). The primary endpoint was ORR. Patients were randomized 1:1 to receive either trastuzumab 4 mg/kg loading dose and then 2 mg/kg/week with weekly vinorelbine (25 mg/m² q week for 8 weeks) or weekly taxanes (paclitaxel 80 mg/m² q week for 8 weeks or docetaxel 35 mg/m² q week for 8 weeks at the investigator's choice). Forty-one patients and 40 patients were randomized to the vinorelbine/trastuzumab and the taxane/trastuzumab arm, respectively (docetaxel n = 24; paclitaxel n = 14, with 2 more patients receiving paclitaxel and carboplatin). Overall, ORR was 51% in the vinorelbine/trastuzumab arm and 40% in the taxane/trastuzumab arm (p = 0.37). Median TTP was not significantly different between the vinorelbine- and taxane-based arms (8.5 versus 6.0 months, p = 0.09). Noteworthy chemotherapy administration delays were more frequent in the vinorelbine containing arm (82% of patients experienced at least 1 week of delay) than the taxane-based arm (overall 60%, 56% for paclitaxel and 63% for docetaxel). With regard to tolerability, anemia and neutropenia were more common with vinorelbine treatment. Alopecia, rash, and nail changes were reported to be more frequently associated with taxane-containing therapy. Among patients treated with docetaxel, 2 had fluid retention syndrome and 5 hyperlacrimation. In the vinorelbine arm, 2 patients went off study for cardiac toxicity. The authors concluded that either weekly vinorelbine/trastuzumab or weekly taxane/trastuzumab are active and feasible and can be considered for the first-line treatment of HER-2 overexpressing MBC patients, even if some caution is required when interpreting these results due to the small proportion of patients included leading to the early termination of the study.

A recent phase III trial was conducted randomizing 118 MBC patients to receive docetaxel on an every-3-week versus weekly basis (Rivera et al 2008). Fifty-nine patients received docetaxel 75 mg/m² every 3 weeks and 59 docetaxel 35 mg/m² for 3 consecutive weeks with 1 week of rest. ORR was 35.6% for the 3-week versus 20.3% for the weekly schedule. No statistically significant difference was observed both in terms of progression-free survival (5.7 months versus 5.5, p = 0.46) and OS (18.3 versus 18.6 months, p = 0.34). A significantly higher toxicity rate, G3/4, was found in the every-3-week treatment arm versus the weekly treatment arm (88.1% versus 55.9%, respectively; p = 0.0001). The trial was terminated early after an interim analysis performed in June 2005 because of a slow accrual rate.

Due to the early termination this study was significantly underpowered even in the authors' opinion, so that it remains unknown whether a larger phase III study could demonstrate

differences in OS and/or progression-free survival. Nevertheless, modest increases in response rate are unlikely to affect OS in patients with advanced MBC.

Conclusion

Since the main goal of MBC management remains palliation, maximizing the antitumor activity and maintaining a favorable toxicity profile appears of paramount relevance in this setting. To date, combinations containing the taxanes represent the standard of care for first-line treatment of these patients. Both docetaxel and paclitaxel can be administered weekly, achieving comparable efficacy results with lower toxicity compared with standard schedules (Zimatore et al 2002).

Particularly, several docetaxel-containing schedules and associations have been tested: overall, weekly, rather than the standard every-3-week dosing can provide good efficacy results and better tolerability, even in heavily pretreated patients with refractory disease and/or in elderly/poor PS women. Unfortunately because there is a great difference between the various experimented weekly schedules (ie, d1,8 q21 or d1,8,15 q28 or 6 consecutive weeks) and the doses employed are vary greatly as well (range from 25 to 40 mg/m^2), it is not possible to draw any definitive conclusion on which is the best dose and timing of administration.

Reviewing the main phase II studies results, it has been highlighted that the obtained ORR can vary between 26% and 86% or 20% and 73% with docetaxel as a single agent or in combination, respectively, depending on doses, associations, and line of treatment.

Furthermore, the lower incidence of severe hematologic toxicities and acute non-hematologic side-effects allows its use in most MBC patients both as single-agent and as part of combination regimens.

The association with biological agents (trastuzumab, bevacizumab) represents a promising therapeutic option given the favorable toxicity profile of these drugs.

Overall, published data support the administration of weekly docetaxel for the treatment of MBC patients even with the lack of data from phase III randomized trials, and keeping in mind the drawbacks of weekly regimens (eg, more frequent hospital visits).

The choice of the best docetaxel weekly schedule in patients with MBC should be based on patient characteristics and on the risk of developing toxic effects. In elderly or unfit patients weekly docetaxel could be preferred.

Disclosures

The authors have no conflicts of interest to disclose.

References

Aihara T, Kim Y, Takatsuka Y. 2002. Phase II study of weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol*, 13:286–92.

Brenner H, Gondos A, Arndt V. 2007. Recent major progress in long-term cancer patient survival disclosed by modeled period analysis. *J Clin Oncol*, 25:3234–80.

Brianoulis E, Karavasilis V, Anastasopoulos D, et al. 1999. Weekly docetaxel in minimally pretreated cancer patients: a dose-escalation study focused on feasibility and cumulative toxicity of long-term administration. *Ann Oncol*, 10:701–6.

Brugnatelli S, Durova M, De Bella MT, et al. 2002. Weekly administration of gemcitabine plus docetaxel in patients with advanced breast cancer: a phase I study. *Oncology*, 62:33–8.

Burstein HJ, Harris LN, Marcom PK, et al. 2003. Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. *J Clin Oncol*, 21:2889–95.

Burstein HJ, Keshaviah A, Baron AD, et al. 2007. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. *Cancer*, 110:965–72.

Burstein HJ, Manola J, Younger J, et al. 2000. Docetaxel administered on a weekly basis for metastatic breast cancer. *J Clin Oncol*, 18:1212–9.

Chan S, Friedrichs K, Noel D, et al. 1999. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol*, 17:2341–54.

Colozza M, de Azambuja E, Personeni N, et al. 2007. Achievements in systemic therapies in the progenomic era in metastatic breast cancer. *Oncologist*, 12:253–70.

Cortes JE, Pazdur R. 1995. Docetaxel. *J Clin Oncol*, 13:2643–55.

D'Andrea GM, Seidman AD. 1997. Docetaxel and paclitaxel in breast cancer therapy: present status and future prospects. *Semin Oncol*, 24(Suppl 13): S13-27–S13-44.

D'Hondt R, Paridaens R, Wildiers H, et al. 2004. Safety and efficacy of weekly docetaxel in frail and/or elderly patients with metastatic breast cancer: a phase II study. *Anticancer Drugs*, 15:341–6.

Esteva FJ, Valero V, Booser D, et al. 2002. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*, 20:1800–8.

Findlay BP, Walker-Dilks C. 1998. Epirubicin, alone or in combination chemotherapy, for metastatic breast cancer. Provincial Breast Cancer Disease Site Group and the Provincial Systemic Treatment Disease Site Group. *Cancer Prev Control*, 2:140–6.

Ford HE, Yap YS, Miles DW, et al. 2006. A phase II study of weekly docetaxel in patients with anthracycline pretreated metastatic breast cancer. *Cancer Chemother Pharmacol*, 58:809–15.

Frasci G, Comella P, D'Aiuto G, et al. 2000. Weekly docetaxel plus gemcitabine or vinorelbine in refractory advanced breast cancer patients: a parallel dose-finding study. Southern Italy Cooperative Oncology Group (SICOG). *Ann Oncol*, 11:367–71.

Gheni D, Wilcken N, Simes J, et al. 2005. Taxane containing regimens for metastatic breast cancer. *Cochrane Database Syst Rev*, (2):CD003366.

Ghosn M, Farhat FS, Kattan JG, et al. 2008a. Navcap (vinorelbine and capecitabine) versus navcap followed by weekly docetaxel as first-line treatment in metastatic breast cancer patients: A randomized multicenter phase II trial. *Proc Am Soc Clin Oncol*, 26:1119a.

Ghosn M, Kattan J, Farhat F, et al. 2008b. Sequential vinorelbine-capecitabine followed by docetaxel in advanced breast cancer: long-term results of a pilot phase II trial. *Cancer Chemother Pharmacol*, 62:11–8.

Hainsworth JD, Burris HA 3rd, Erland JB, et al. 1998. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol*, 16:2164–8.

Hainsworth JD, Burris HA 3rd, Yardley DA, et al. 2001. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a Minnie Pearl Cancer Research Network phase II trial. *J Clin Oncol*, 19:3500–5.
Hayat MJ, Howlader N, Reichman ME, et al. 2007. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist*, 12:20–37.
Holmes FA, Walters RS, Theriault RL, et al. 1991. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst*, 83:1797–805.
Hotchkiss KA, Ashton AW, Mahmood R, et al. 2002. Inhibition of endothelial cell function in vitro and angiogenesis in vivo by docetaxel (Taxotere): association with impaired repositioning of the microtubule organizing center. *Mol Cancer Ther*, 1:1191–200.
Ibrahim T, Serra P, Vertogen B, et al. 2007. Doxorubicin (Dox), cyclophosphamide (Cyc) and weekly docetaxel (Doc) as first-line treatment of advanced breast cancer (ABC). *Proc Am Soc Clin Oncol*, 25(18S):11516a.
Ito Y, Aiba K, Horikoshi N, et al. 2001. Dose-finding phase I study of stimultaneous weekly infusion with doxorubicin and docetaxel in patients with advanced breast cancer. *Int J Clin Oncol*, 6:242–7.
Jackisch C, Fibuch H, Knuth A, et al. 2000. Phase-II trial of docetaxel weekly as dose dense treatment in metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol*, 19:417a.
Kornek GV, Ulrich-Pur H, Penz M, et al. 2001. Treatment of advanced breast cancer with vinorelbine and docetaxel with or without human granulocyte colony-stimulating factor. *J Clin Oncol*, 19:621–7.
Kourounis C, Agelaki S, Mavroudis D, et al. 2000. A dose escalation study of weekly docetaxel in patients with advanced solid tumors. *Cancer Chemother Pharmacol*, 46:488–92.
Loeffler TM, Freund W, Droge C, et al. 1998. Activity of weekly Taxotere in patients with metastatic breast cancer [abstract]. *J Clin Oncol*, 17:abstr 113.
Luck HJ, Dorndé S, Claubitz M, et al. 1997. Phase I study of weekly docetaxel (Taxotere) in heavily pretreated breast cancer patients. *Eur J Cancer*, 33(s8):s158 (abstract 703).
Marty M, Cognetti F, Maraninchi D, et al. 2005. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*, 23:4265–74.
Meier CR, Illiger HJ, Steder M, et al. 2004. Weekly vinorelbine (VIN) vs weekly docetaxel (DOC) for metastatic breast cancer failing anthracyclines. Planned interim analysis of a randomized trial. *Proc Am Soc Clin Oncol*, 22(14s):734a.
Miles D, Chan A, Romieu G, et al. 2008. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. *J Clin Oncol*, 26:1011a.
Miller K, Wang M, Gralow J, et al. 2007. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*, 357:2666–76.
Mrozek E, Ramaswamy B, Young D, et al. 2006. Phase II study of weekly docetaxel and capecitabine in patients with metastatic breast cancer. *Clin Breast Cancer*, 7:141–5.
Nabholtz JM, Gelmon K, Bontenbal M, et al. 1996. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol*, 14:1858–67.
Nabholtz JM, Thuerlimann B, Burwoda WR, et al. 1997. Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer. *Oncology (Williston Park)*, 11(8 Suppl 8):25–30.
Nistico C, Cognetti F, Frontini L, et al. 2005. Weekly docetaxel in pretreated metastatic breast cancer patients: a phase I–II study. *Oncology*, 68:356–63.
O'Brien ME, Leonard RC, Barrett-Lee PJ, et al. 1999. Docetaxel in the community setting: an analysis of 377 breast cancer patients treated with docetaxel (Taxotere) in the UK. UK Study Group. *Ann Oncol*, 10:205–10.
Palmeri S, Vaglica M, Spada S, et al. 2005. Weekly docetaxel and gemcitabine as first-line treatment for metastatic breast cancer: results of a multicenter phase II study. *Oncology*, 68:438–45.
Paridaens R, Biganzoli L, Bruning P, et al. 2000. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer Randomized Study with cross-over. *J Clin Oncol*, 18(4):724–33.
Peacock NW, Infante JR, Yardley DA, et al. 2008. Phase II trial of weekly docetaxel, vinorelbine, and trastuzumab in the first-line treatment of patients (pts) with HER2-positive metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol*, 26:1032a.
Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. 2005. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*, 353:1659–72.
Raab G, Brugger W, Harbeck N, et al. 2002. Multi-center randomized phase II study of docetaxel (Doc) given q3w vs. q1wk plus trastuzumab (Tra) as first line therapy for HER2 overexpressing adjuvant anthracycline pretreated metastatic breast cancer (MBC). *Breast Cancer Res Treat*, 76 (Suppl 1):S114 a.
Raff JP, Rajdev L, Malik U, et al. 2004. Phase II study of weekly docetaxel alone or in combination with trastuzumab in patients with metastatic breast cancer. *Clin Breast Cancer*, 4:420–7.
Ramaswamy B, Elias AD, Kelbick NT, et al. 2006. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. *Clin Cancer Res*, 12:3124–9.
Ramos M, Gonzalez-Agüero A, Armendo M, et al. 2003. Weekly docetaxel as second-line therapy for patients with advanced breast cancer resistant to previous anthracycline treatment. *J Chemother*, 15:192–7.
Rawlin PM, Harris HA 3rd, Cook G, et al. 1995. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. *J Clin Oncol*, 13:2879–85.
Ringel I, and Horwitz SB. 1991. Studies with RP 56976 (taxotere): a semisynthetic analogue of taxol. *J Natl Cancer Inst*, 83:288–91.
Rivera E, Mejia JA, Arun BK, et al. 2008. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer*, 112:1455–61.
Romond EH, Perez EA, Bryant J, et al. 2005. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*, 353:1673–84.
Rosati MS, Raimondi C, Quadrini S, et al. 2008. WALT trial (Phase I-II): Weekly non-pegylated liposomal anthracycline and taxane combination in first-line breast cancer chemotherapy. *J Clin Oncol*, 26:1097a.
Salminen E, Bergman M, Hahtala S, et al. 1999. Docetaxel: standard recommended dose of 100 mg/m(2) is effective but not feasible for some metastatic breast cancer patients heavily pretreated with chemotherapy-A phase II single-center study. *J Clin Oncol*, 17:1127.
Sedlky L, Saad I, Hashem B, et al. 2002. Weekly docetaxel vs. every 3-week in advanced breast cancer: results of a pilot comparative study. *Proc Am Soc Clin Oncol*, 20:2013a.
SEER. 2008. Accessed 04 February 2008. *URL*: http://apps.nccd.cdc.gov/uscs/Table.aspx?Group=3&Year=2004&Display=n.
Seidman AD, Reichman BS, Crown JP, et al. 1995a. Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol*, 13:1152–9.
Seidman AD, Tiersten A, Hudis C, et al. 1995b. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol*, 13:2575–81.
Slamon DJ, Leyland-Jones B, Shak S, et al. 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*, 344:783–92.
Sledge GW, Neuberg D, Bernardo P, et al. 2003. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol*, 21:588–92.
Stemmler HJ, Gutschow K, Sommer H, et al. 2001. Weekly docetaxel (Taxotere) in patients with metastatic breast cancer. *Ann Oncol*, 12:1393–8.

Sternmler J, Muir W, Stauch M, et al. 2005. High efficacy and low toxicity of weekly docetaxel given as first-line treatment for metastatic breast cancer. *Oncology*, 68:71–8.

Stockler M, Wilcken NR, Ghersi D, et al. 2000. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev*, 26:151–68.

Tabernero J, Climent MA, Lluch A, et al. 2004. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. *Ann Oncol*, 15:1358–65.

Tolaney KL, Thor AD, Johnson DH, et al. 2004. Docetaxel combined with trastuzumab is an active regimen in HER-2 3+ overexpressing and fluorescent in situ hybridization-positive metastatic breast cancer: a multi-institutional phase II trial. *J Clin Oncol*, 22:1071–7.

Tomiak E, Piccart MJ, Kerger J, et al. 1994. Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. *J Clin Oncol*, 12:1458–67.

Valero V. 1997. Docetaxel as single-agent therapy in metastatic breast cancer: clinical efficacy. *Semin Oncol*, 24(Suppl 13):S13-1-S-8.

Valero V, Holmes FA, Walters RS, et al. 1995. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol*, 13:2886–94.

Waterhouse DM, Mainwaring M, Barton J, et al. 2008. Phase II pilot results of imatinib mesylate with weekly docetaxel in metastatic breast cancer. *Proc Am Soc Clin Oncol*, 26:1090a.

Wenzel C, Hussian D, Hartsch R, et al. 2004. Preoperative therapy with epidoxorubicin and docetaxel plus trastuzumab in patients with primary breast cancer: a pilot study. *J Cancer Res Clin Oncol*, 130:400–4.

Wenzel C, Locker GJ, Planchnig U, et al. 2002. Phase I/II trial of weekly epidoxorubicin and docetaxel (wED) in the neoadjuvant and palliative treatment of patients with breast cancer. *Cancer Chemother Pharmacol*, 50:155–9.

Zimatore M, Danova M, Vassallo E, et al. 2002. Weekly taxanes in metastatic breast cancer (review). *Oncol Rep*, 9:1047–52.

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Ruolo dei trattamenti loco-regionali nelle pazienti con metastasi epatiche da carcinoma della mammella

Cristina Raimondi[1], Marco Danova[2], Sofia Chatzileontiadou[2], Laura Palmeri[1], Alessandro Vercelli[3], Sergio Palmeri[1]

Riassunto. Le metastasi epatiche sono presenti in circa il 18% dei casi di carcinoma della mammella: sebbene alcune pazienti abbiano una sopravvivenza superiore ai 25 mesi, la sopravvivenza mediana dopo la ormono- o chemioterapia è di 6-14 mesi. Negli ultimi anni, nuovi regimi di chemioterapia e le terapie molecolari mirate hanno dato ragione agli oncologi di credere che la malattia metastatica possa essere eradicata, o almeno controllata per lunghi periodi di tempo. Allo scopo di migliorare la sopravvivenza, è stato dato valore ai trattamenti loco-regionali come la resezione epatica (HR) e l'ablazione a radio-frequenza (RFA), che sono stati associati con risultati migliori in pazienti selezionate. Questa rassegna valuta il ruolo e l'efficacia di due approcci loco-regionali in una prospettiva multidisciplinare nel trattamento delle metastasi – singole o multiple, limitate al fegato – da carcinoma della mammella. Sono stati valutati l'impiego e l'effetto della resezione epatica e dell'ablazione a radiofrequenza sulla scorta dei dati disponibili in letteratura, allo scopo di determinare il loro impatto sui risultati di sopravvivenza. Essi suggeriscono che i trattamenti loco-regionali dovrebbero fornire un beneficio significativo in un gruppo selezionato di donne con metastasi epatiche da carcinoma della mammella, ma il ruolo di questi trattamenti locali nel trattamento multimodale delle metastasi epatiche rimane controverso. Può essere detto, in generale, che i trattamenti loco-regionali possono migliorare la sopravvivenza globale, con nessuna mortalità e meno del 20% di morbilità in pazienti a basso rischio chirurgico; in genere, essi dovrebbero essere considerati trattamenti cito-riduttivi, e come tali, necessitano sempre di essere integrati con le terapie sistemiche.

Parole chiave. Ablazione a radiofrequenza, carcinoma della mammella, metastasi epatiche, resezione epatica, trattamento loco-regionale.

Summary. *Role of loco-regional treatments for patients with breast cancer liver metastases.*

Breast cancer liver metastases (BCLM) are not uncommon (about 18% of cases): although some patients have been reported as still living after 25 months, median survival after hormonal- or chemotherapy is 6-14 months. In recent years, new chemotherapy regimens and molecular targeted therapies have given medical oncologists reason to believe that metastatic disease can be eradicated, or at least controlled for prolonged periods. In an attempt to improve survival, consideration has also been given to loco-regional treatments such as hepatic resection and radio-frequency ablation, which have been associated with better outcomes in selected patients. This review considers the role of two loco-regional approaches in a multidisciplinary perspective in the treatment of single or multiple breast cancer metastases limited to the liver. An expanded role for hepatic resection and ablation is being investigated. We assessed available data in the literature to determine their role on survival outcomes. They suggest that loco-regional treatments might be of significant benefit in a selected group of women with BCLM, but the role of these local treatments in multimodality treatment of liver metastases remains controversial. It can generally be said that loco-regional treatments can improve overall survival, with no mortality and less than 20% morbidity in patients at low surgical risk; however, they should only be considered cytoreductive treatments and, as such, always need to be integrated with systemic therapy.

Key words. Liver metastases from breast cancer, hepatic resection, loco-regional treatment, radio-frequency ablation.

[1]Oncologia Medica, Università e Policlinico Giaccone, Palermo; [2]Struttura Complessa di Oncologia Medica; [3]Istituto di Radiologia, Università e Fondazione IRCCS Policlinico S. Matteo, Pavia.
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Introduzione

Il carcinoma della mammella è al terzo posto come frequenza nel mondo (23%), dopo il tumore del polmone e quello gastrico. È la quinta causa di morte tra tutti i tumori. Rappresenta il 14,1% del totale di morti per cancro tra le donne[1]. Secondo l'Organizzazione Mondiale della Sanità, nel 2004, il carcinoma della mammella è stato diagnosticato in più di 1,2 milioni di soggetti. Può metastatizzare in ogni parte del corpo, ma le regioni più comunemente colpite, in ordine di frequenza, sono le ossa, il polmone e il fegato. Il carcinoma della mammella metastatico può essere una malattia altamente variabile. È stato riportato che nel 5-12% delle pazienti, le metastasi risultano confinate al fegato[2]. Il carcinoma della mammella ha riguardato un numero aumentato di donne negli anni recenti a causa di alcuni fattori, quali la diffusione della mammografia, ma le percentuali di mortalità si sono ridotte grazie ai miglioramenti nella terapia adiuvante e all'uso di nuovi agenti biologici. D'altra parte, l'incidenza del carcinoma della mammella metastatico è rimasta immodificata e la sopravvivenza delle pazienti con malattia a distanza non è sostanzialmente migliorata. La sopravvivenza mediana per le pazienti con carcinoma della mammella metastatico è approssimativamente di 2 anni. Di norma, il trattamento chirurgico non è utilizzato. La chemioterapia e l'ormonoterapia rappresentano lo standard di cura, ma la progressione della malattia dopo ogni risposta alle terapie sistemiche è generalmente inevitabile od è infrequente una modifica nel tipo di risposta. La chemioterapia ritarda la progressione e prolunga la sopravvivenza, ma raramente cura la malattia. Sebbene queste terapie abbiano raggiunto una risposta nel 40-70% dei casi, la sopravvivenza media non aumenta od è compresa tra 4 e 17 mesi[3].

Inoltre lo sviluppo delle metastasi epatiche non correla con l'età, né con lo stato menopausale, né con la misura del tumore primitivo, con lo stato dei linfonodi regionali o la lunghezza dell'intervallo libero da malattia. La sopravvivenza mediana riportata dopo la prima recidiva di metastasi epatica è compresa tra 1 e 15 mesi[4]. L'incidenza di metastasi isolate al fegato all'autopsia è di 5-12%[5] (tabella 1).

La storia naturale di questa condizione è scarsamente definita e il trattamento rimane controverso, perché generalmente è considerata una malattia sistemica. Comunque, in una piccola proporzione di pazienti con carcinoma della mammella (1%), le metastasi epatiche focali sono l'unico segno di disseminazione della malattia con nessuna evidenza di malattia extraepatica[6].

Tabella 1. *Metastasi epatiche da carcinoma della mammella.*

Frequenza	18% dei tumori mammari metastatici
Singola sede di metastasi	5-12% delle pazienti
Incidenza	50% delle pazienti in IV stadio
Sopravvivenza mediana	1-15 mesi
Sopravvivenza mediana in pazienti non trattate	4-8 mesi
Mortalità per insufficienza epatica	20% dei casi

Le metastasi epatiche si sviluppano approssimativamente nel 18% di donne con tumore della mammella e sono tipicamente associate con localizzazione secondarie in altri organi, indicando una malattia avanzata e una prognosi scarsa. Il fegato è l'organo più comune per la recidiva a distanza, dopo l'osso e il polmone.

Questa potrebbe essere una condizione più favorevole e suscettibile di approccio più aggressivo che include un trattamento loco-regionale con intento curativo. Negli ultimi anni, nuovi regimi di chemioterapia e terapie molecolari mirate hanno dato ragione agli oncologi di credere che la malattia metastatica possa essere aradicata, o almeno controllata per lunghi periodi di tempo[7]. La sopravvivenza mediana in gruppi selezionati di pazienti con carcinoma della mammella metastatico trattato con ormonoterapia e/o chemioterapia oppure con terapia di supporto è compresa tra 6 e 14 mesi, con un'occasionale sopravvivenza oltre due anni dopo la diagnosi.

La resezione epatica (HR) e la ablazione a radiofrequenza (RFA) offrono la sola possibilità di cura nelle pazienti con tumori epatici primitivi e secondari; tra il 25% e il 38% di pazienti con metastasi epatiche da tumore del colon retto sono stati trattati con la chirurgia in assenza di malattia extraepatica[8]. Quando queste pazienti possono essere rese clinicamente libere da malattia con i trattamenti locali (chirurgia o radiazione), esiste una possibilità di raggiungimento di remissione completa dalla chemioterapia e possono rimanere libere da malattia per lunghi periodi di tempo.

Da questa prospettiva multidisciplinare, è stato attivamente valutato il ruolo della resezione epatica e dell'ablazione. Sebbene la maggior parte dei medici guardi con rassegnazione le metastasi epatiche da carcinoma della mammella e tenti una palliazione con l'ormono- e la chemioterapia, alcuni hanno tentato trattamenti aggressivi loco-regionali includendo **la resezione epatica e l'ablazione a radiofrequenza.**

Poiché la mortalità e la morbilità associate con questi trattamenti si sono drasticamente ridotte nell'ultimo decennio, si è diffusa l'indicazione in una varietà di tumori metastatici, sebbene l'efficacia rimanga controversa. Le migliori candidate per la resezione non devono avere malattia metastatica extraepatica, hanno un buon performance status e un lungo intervallo libero da malattia dopo il trattamento del tumore primitivo (figura 1). Solo un piccolo numero di studi retrospettivi ha esaminato i risultati delle pazienti con metastasi limitate al fegato trattate con chirurgia, e il numero delle pazienti in questi studi è relativamente esiguo. Non di meno c'è evidenza che la chirurgia con o senza chemioterapia nel trattamento di tali pazienti può significativamente aumentare la sopravvivenza.

Il ruolo della RFA dovrebbe essere attentamente valutato in gruppi più ampi di soggetti. Al momento, l'intervento dovrebbe essere riservato alle pazienti che non possono subire una resezione o dovrebbe essere utilizzato come adiuvante alla resezione.

A causa del limitato numero di pazienti con metastasi epatiche per le quali i dati sono disponibili, del piccolo ed eterogeneo numero di studi, degli scarsi dati sui fattori prognostici per sopravvivenze dopo i trattamenti loco-regionali, l'interpretazione dei risultati risulta difficile[8].

Diagnostica per immagini delle metastasi epatiche

Gli obiettivi della diagnostica per immagini del fegato, in oncologia sono: la diagnosi delle malattie epatiche, la caratterizzazione delle lesioni epatiche, la valutazione della risposta al trattamento e la visualizzazione dell'anatomia vascolare per un programma chirurgico. È importante distinguere l'utilità delle varie modalità di imaging.

L'ECOGRAFIA è economica e facilmente disponibile. È altamente sensibile nel differenziare una cisti da una lesione solida del fegato. La sensibilità riportata varia dal 40 al 70%. Comunque, non è così sensibile come la TC o la Risonanza Magnetica nel visualizzare le lesioni solide, focali del fegato. Le principali limitazioni dell'ecografia sono la operatore-dipendenza, l'incapacità di visualizzare lesioni <1 cm e la bassa specificità. Allo stesso modo, le pseudo-lesioni come le infiltrazioni locali steatosiche o le aree indenni da steatosi sono a volte difficili da differenziare dalle altre lesioni patologiche del fegato. La recente aggiunta all'ecografia del mezzo di contrasto si è mostrata promettente nella caratterizzazione dei vari tumori epatici.

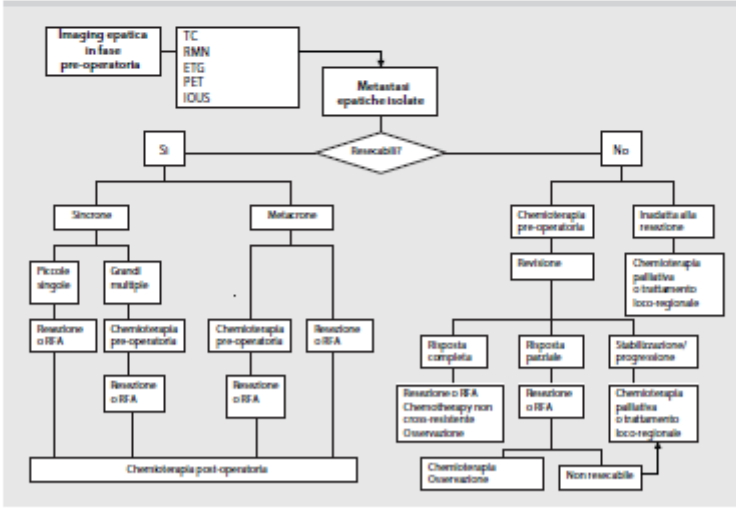

Figura 1. Metastasi epatiche isolate da carcinoma della mammella; criteri di resecabilità e trattamenti loco-regionali.

Inoltre, l'ecografia intraoperatoria (IOUS) può identificare le metastasi focali <3 mm non visibili.

■ LA TOMOGRAFIA COMPUTERIZZATA (TC) offre la migliore risoluzione spaziale. È l'ideale esame di screening per l'addome e la pelvi. Recenti avanzamenti nella tecnologia TC (come la "helical TC") hanno migliorato notevolmente la performance della TC in termini di velocità di acquisizione, risoluzione e capacità, durante le varie fasi di presa del contrasto, per valutare lesioni epatiche focali e fegato normale. Le sue limitazioni includono la necessità di un'alta dose di radiazioni e una bassa sensibilità per la visualizzazione e la caratterizzazione di lesioni <1 cm. È, inoltre, controindicata in pazienti con una storia di anafilassi per il mezzo di contrasto e di insufficienza renale.

■ RISONANZA MAGNETICA (RM): le sue principali applicazioni includono la caratterizzazione dei tumori epatici, la differenziazione tra le pseudolesioni e le metastasi. Ha un'alta risoluzione spaziale, una migliore sensibilità di contrasto e l'assenza di radiazioni ionizzanti. La RM con mezzo di contrasto (per esempio DTPA) può essere usata con sicurezza. La RM è superiore alla TC nella visualizzazione e nella caratterizzazione delle lesioni. Le principali limitazioni includono un costo elevato e la lunga procedura di esecuzione.

■ LA TOMOGRAFIA AD EMISSIONE DI POSITRONI (PET) è emersa come un importante strumento diagnostico per la valutazione delle metastasi. Un'elevata attività metabolica nel tessuto tumorale è accompagnata da un'aumentata captazione di glucosio rispetto al tessuto normale circostante. Questa procedura è altamente sensibile e capace di visualizzare l'intero corpo per la ricerca di malattia metastatica extraepatica; tuttavia, ogni area focale di aumentato metabolismo può dare risultati falsi positivi. I principali svantaggi includono il suo alto costo, la scarsa localizzazione delle lesioni e la limitata sensibilità per le lesioni <1 cm. La PET-TC combina i vantaggi della TC con la capacità funzionale della PET grazie alla fusione delle due tecniche ed all'acquisizione di immagini allo stesso tempo.

▶ La scelta delle migliori tecniche di imaging dipende dal quesito clinico. In generale, l'ecografia e la TC rimangono le prime metodiche per la valutazione precoce e la caratterizzazione della maggior parte delle pazienti con sospette metastasi epatiche. La selezione per un programma chirurgico o per altri approcci loco-regionali è il principale obiettivo della diagnostica per immagini preoperatoria.

La TC è la modalità di imaging di scelta per valutare la risposta tumorale dopo resezione o ablazione a radiofrequenza. La presenza di "enhacement" nodulare attorno ai margini chirurgici indica recidiva. La TC con mezzo di contrasto è utile nel valutare la completa necrosi tumorale dopo la RFA. Una questione irrisolta è la ristadiazione dopo la chemioterapia.

Dopo una prolungata chemioterapia, il parenchima epatico diventa steatosico. La riduzione delle metastasi epatiche può essere nascosta dai cambiamenti in ecogenicità agli ultrasuoni o dalla densità alla TC. Piccole metastasi possono non essere visualizzate dalle usuali tecniche di imaging.

Comunque, i recenti progressi nella diagnostica per immagini del fegato hanno migliorato la capacità di queste tecniche di visualizzare una remissione completa patologica delle metastasi[9].

Resezione epatica

Sebbene siano stati fatti significativi progressi nel trattamento multimodale delle pazienti con metastasi epatiche da carcinoma della mammella, incluso l'uso di più efficaci chemioterapie sistemiche, terapie ormonali (inibitori dell'aromatasi) ed agenti biologici mirati (trastuzumab, bevacizumab), lo sviluppo di metastasi a distanza continua ad essere associato ad una scarsa prognosi. Ciò nonostante, due sono le principali ragioni per cui le pazienti con metastasi epatiche da carcinoma della mammella sono raramente candidate ad una valutazione chirurgica. La prima è che la maggior parte delle pazienti ha anche metastasi extraepatiche, considerate controindicazione alla resezione epatica. L'altra ragione è correlata alla percezione che il carcinoma della mammella con metastasi epatiche ha una prognosi particolarmente infausta. In alcuni casi, i trattamenti con un profilo di tossicità minimo sono da preferirsi ai trattamenti più aggressivi come la chemioterapia sistemica e la resezione epatica.

Sulla base di questi fattori, gli studi che esaminano il ruolo della resezione epatica contengono pochi casi. Negli anni passati, **la resezione epatica si è evoluta come un trattamento sicuro e potenzialmente curativo per le metastasi epatiche.** Da quando la mortalità e la morbilità associata con la resezione del fegato si è ridotta significativamente nell'ultimo decennio, si è diffusa l'indicazione per la chirurgia in una varietà di condizioni metastatiche. **La resezione epatica potrebbe essere considerata come un trattamento adiuvante o neoadiuvante alla terapia sistemica in pazienti selezionate**[46].

Il razionale per il trattamento chirurgico delle metastasi epatiche è il seguente: attualmente non ci sono terapie efficaci per le metastasi epatiche; recenti progressi nella chirurgia epatica hanno reso la metastasectomia un'operazione molto più sicura, specialmente quando la funzione epatica è normale; recenti progressi nelle tecniche di imaging hanno reso le metastasi epatiche più facilmente valutabili e la maggior parte delle pazienti può essere controllata routinariamente in follow-up con l'ecografia addominale e/o con la TC, come candidate suscettibili ad essere selezionate per il trattamento chirurgico (figura 2). Non solo le metastasi epatiche causano un'alterazione della funzione epatica, ma possono essere fonte di altre metastasi a distanza[47]. La resezione epatica non può essere considerata come un trattamento definitivo od isolato, bensì come intervento citoriduttivo.

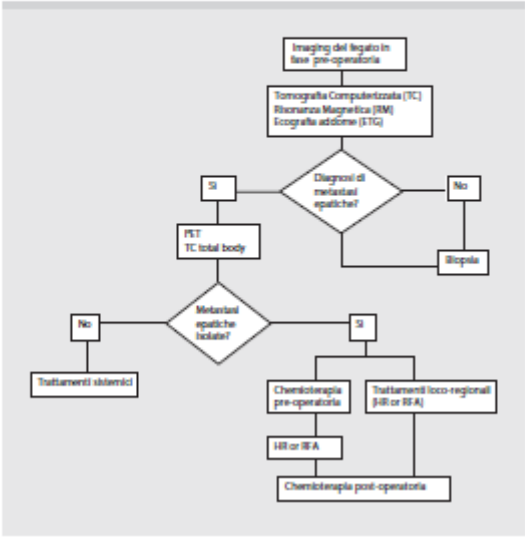

Figura 2. Metastasi epatiche isolate da carcinoma della mammella: flow-chart decisionale.

La riduzione del volume tumorale totale fino a dimensioni che ne consentano il trattamento diminuisce sostanzialmente la possibilità che le cellule tumorali sviluppino farmacoresistenza, configurandosi quale utile aggiunta alla terapia sistemica nel migliorare i risultati. Le indicazioni al trattamento chirurgico sono controverse (tabella 2), ma i risultati mostrano che metastasi stabili possano essere rescate con successo.

Lo sviluppo di chemioterapia e le terapie molecolari target, insieme con nuove modalità come l'ablazione a radiofrequenza, più affinate tecniche di imaging preoperatorie e migliori risultati operatori hanno esteso le indicazioni per la resezione epatica e migliorato la sopravvivenza. Inoltre, le percentuali di mortalità operatoria sono costantemente ridotte a meno del 5%, con un'accettabile morbilità.

Riportiamo gli studi più ampi di resezioni epatiche (tabella 3)[10-24].

Le metastasi epatiche isolate dal carcinoma della mammella sono rare, ma alcune volte la terapia sistemica riesce a stabilizzare la malattia solo in questo organo. Tre studi retrospettivi hanno dimostrato una percentuale di sopravvivenza globale a tre anni compresa tra 49% e 51%[7].

■ Elias et al.[10] hanno trattato con resezione epatica 54 pazienti affette da carcinoma della mammella con metastasi epatiche come unico sito di malattia metastatica tra il 1986 ed il 2000. La morbilità post-operatoria è stata del 12,9%. Non si è verificata nessuna mortalità post-operatoria. Dopo un follow-up mediano di 32 mesi la sopravvivenza mediana è stata di 34±9 mesi, con percentuali di sopravvivenza globale a 3 ed a 5 anni del 50% e del 34%, e con percentuali di sopravvivenza libera di malattia a 3 ed a 5 anni del 42% e del 22%, rispettivamente. Il numero delle metastasi epatiche, la presenza di linfonodi ilari e la radicalità della resezione non hanno avuto impatto prognostico significativo.

■ Pocard et al.[11] hanno analizzato un gruppo di pazienti altamente selezionate che sono state sottoposte a resezione epatica. Non c'è stata mortalità post operatoria. 18% di morbilità post-operatoria. Il follow-up mediano è stato di 41 mesi (6-100 mesi).

Tabella 2. *Indicazioni e controindicazioni alla resezione epatica delle metastasi epatiche da carcinoma della mammella.*

	Controindicazioni
1. Tumore primitivo controllato	1. Malattia extraepatica
2. Metastasi limitate al fegato (mts ossee?)	2. Comorbilità (performance status insoddisfacente)
3. Metastasi epatiche completamente resecabili	3. Insufficienza epatica
4. Buon performance status	4. Lesioni multifocali
5. Risposta obiettiva o/e stabilizzazione di malattia dopo chemioterapia preoperatoria, per almeno 3 mesi	5. Invasività (alto rischio operatorio)
	6. elevato costo

La percentuale di sopravvivenza dopo la chirurgia è stata del 90% ad 1 anno del 71% a 3 anni e del 46% a 4 anni. 13 pazienti sono vivo a 4 anni.

■ Selzner et al.[6] hanno dimostrato una sopravvivenza a 5 anni del 22% dopo resezione epatica.

■ Adam et al.[12] hanno rivisto i risultati di 85 pazienti con metastasi epatiche da carcinoma della mammella trattate con resezioni epatiche dal 1984 al 2004. Dopo la resezione epatica, 28 pazienti (33%) hanno sviluppato recidive di metastasi epatiche isolate, 12 di queste erano state trattate con nuova resezione epatica. Al follow-up mediano di 38 mesi, 32 delle 85 pazienti erano vive; la mediana e la sopravvivenza globale a 5 anni erano, rispettivamente di 32 mesi e del 37%. La mediana e la sopravvivenza libera da malattia a 5 anni erano di 20 mesi e del 21%. La risposta alla chemioterapia preoperatoria, la resezione dei margini e la ri-metastasectomia per recidiva intraepatica erano fattori prognostici chiave.

■ Sakamoto et al.[14] hanno analizzato 34 pazienti sottoposte a 35 resezioni per metastasi epatiche tra il 1985 ed il 2003. 15 fattori clinico-patologici sono stati valutati allo scopo di predire la sopravvivenza dopo resezione epatica. La presenza di recidiva extraepatica prima della resezione epatica era il solo fattore prognostico significativo; la percentuale di sopravvivenza a 5 anni delle pazienti senza malattia extraepatica era del 31%. Nessuna paziente è deceduta a causa della chirurgia. La sopravvivenza mediana era di 36 mesi (1-20 mesi). Le percentuali di sopravvivenza globale e libera da malattia a 5 anni erano del 21% e 16% rispettivamente. 4 pazienti sono sopravvissute più di 5 anni. Nessuna paziente che aveva linfonodi ilari è sopravvissuta più di 5 anni. In assenza di malattia extraepatica, la resezione epatica può offrire un'accettabile prognosi; essa potrebbe essere evitata in pazienti selezionate.

■ Thelen et al.[15] hanno condotto uno studio per chiarire la sicurezza e l'efficacia della resezione epatica e per identificare i criteri di selezione delle pazienti. Dal 1988 al 2006 sono state analizzate 39 pazienti. Nessuna delle pazienti è deceduta nel perioperatorio e la percentuale di morbilità è stata del 13%. Le percentuali di sopravvivenza globale a 1, 3 e 5 anni sono state del 77%, 50% e 42% rispettivamente.

Tabella 3. *Studi relativi ai dati di sopravvivenza dopo resezione chirurgica di metastasi epatiche da carcinoma della mammella.*

Autore	Anno	Periodo	N. pazienti	Mortalità postoper. (%)	Sopravvivenza mediana (mesi)	Sopravvivenza 5 anni (%)
Schneebaum et al.[24]	1994	—	6	—	42	—
Lorenz et al.[8,12]	1995	—	8	—	15	12%
Elias et al.[8,12]	1995	'86-'94	21	0	26	22%
Raab et al.[17]	1998	'83-'93	34	3	27	18%
Seifert et al.[8,12]	1999	'85-'97	15	0	57	18%
Santoro et al.[8,12]	2000	'90-'98	15	0	44	38.3%
Kondo et al.[8,12]	2000	'90-'99	6	0	36	40%
Maksan et al.[4]	2000	'84-'98	9	0	—	51%
Selzner et al.[6]	2000	'87-'99	17	6	25	22%
Yoshimoto et al.[18]	2000	'85-'98	25	—	34	—
Pocard et al.[11]	2001	'88-'99	65	0	47	46% (sopravv. a 4 anni)
Carlini et al.[8,12]	2002	'90-'99	17	0	53	46%
Elias et al. [10]	2003	'86-'00	54	0	34±9	34%
Vlastos et al.[20]	2004	'91-'02	31	0	63	61%
Sakamoto et al.[14]	2005	'85-'03	34	0	36	21%
D'Annibale et al.[8,12]	2005	'84-'99	18	0	32	30%
Ercolani et al.[8,12]	2005	'90-'03	21	0	42	25%
Adam et al.[12]	2006	'84-'04	85	0	32	37%
Thelen et al.[15]	2006	'88-'06	39	0	-	42%

Le manifestazioni metastatiche precedenti alla resezione epatica, l'invasione vascolare e i margini di resezione rilevati hanno influito in maniera statisticamente significativa sulla sopravvivenza. L'analisi multivariata ha identificato solo i margini di resezione come fattore prognostico indipendente per la sopravvivenza.

Er O, Hortobagyi, Arun et al.[16] hanno condotto un'analisi retrospettiva per descrivere il decorso clinico di 2193 pazienti con carcinoma della mammella con solo metastasi epatiche che erano state trattate con doxorubicina/ciclosfamide o protocolli di chemioterapia contenenti taxani, tra il 1973 ed il 2003, al M.D.Anderson Cancer Center. Il follow-up mediano delle pazienti era di 52 mesi. La percentuale di risposta obiettiva globale era del 66,4%; il 16,4% delle pazienti ha raggiunto una risposta completa. Il tempo mediano alla progressione era di 14 mesi. Le percentuali di sopravvivenza libere da progressione erano del 56% e del 30% a 12 e 24 mesi, rispettivamente. La sopravvivenza globale mediana era di 25 mesi. 16 pazienti (12,1%) sono sopravvissuti più di 60 mesi.

C'è una relazione statisticamente inversa tra un alto livello di lattato deidrogenasi ed il raggiungimento di una risposta completa ($p<0,05$).

L'età ≥50 anni, l'estensione delle metastasi epatiche, il performance status ed i livelli di lattato deidrogenasi e albumina sono significativamente correlati alla sopravvivenza libera da progressione ($p<0,05$).

Gli anni dalla diagnosi di metastasi epatiche, l'estensione delle metastasi, il performance status ed i livelli di albumina sono significativamente correlati con la sopravvivenza globale ($p<0,05$).

Questa analisi retrospettiva ha dimostrato che le pazienti con metastasi epatiche isolate hanno alte percentuali di risposte obiettive e sono stati ottenuti incoraggianti risultati per la sopravvivenza mediana con gli agenti citotossici attualmente disponibili.

La resezione epatica dovrebbe in ogni caso essere considerata nell'ambito di un approccio terapeutico multidisciplinare per pazienti attentamente selezionate, con la finalità del raggiungimento di risposta completa o ad intento curativo[7]. Il dogma secondo cui la terapia chirurgica non avrebbe un ruolo nel trattamento delle pazienti oncologiche con apparente malattia sistemica non è quindi più valido. Quando si include in un programma di trattamento multimodale, la resezione epatica può oggi essere condotta con basso rischio e, posto che la malattia metastatica sia sensibile alla chemioterapia preoperatoria e che la resezione sia microscopicamente completa, **la terapia chirurgica può essere vista come un trattamento "adiuvante", in combinazione con le terapie sistemiche in pazienti selezionate, fornendo un beneficio in termini di sopravvivenza**[12].

Nonostante i risultati che conseguono alla resezione epatica continuino a migliorare, solo una minoranza di pazienti con metastasi epatiche da carcinoma della mammella sono candidate alla resezione. La resezione rimane il gold standard per i tumori epatici, ma i 2/3 di questi tumori possono essere non resecabili.

Alcune strategie di trattamento loco-regionale sono emerse per incrementare il numero di pazienti eleggibili a terapie dirette al fegato (tabella 4). La scelta della strategia di trattamento dovrebbe essere guidata dalle caratteristiche del tumore: istologia, misura, numero delle lesioni e localizzazione anatomica.

Tabella 4. *Trattamenti loco-regionali delle metastasi epatiche.*

1) Resezione epatica (metastasectomia)
2) Terapie locali ablative (chimiche o termiche)
– Iniezione percutanea di etanolo (PEI)
– Iniezione percutanea di acido acetico (PAI)
– Crioablazione
– Ablazione a radiofrequenza (RFA)
– Terapia di coagulazione con microonde (MCT)
– Ablazione laser (LITT)
– High-intensity focused ultrasound (HIFU).
3) Terapie regionali transarteriose
– Chemioterapia transarteriosa
– Embolizzazione transarteriosa
– Chemioembolizzazione transarteriosa (TACE)
– Radioembolizzazione

Attualmente la TACE (chemoembolizzazione transarteriosa)[42], l'iniezione di etanolo e l'ablazione a radiofrequenza (RFA) sono le modalità di trattamento del fegato più largamente utilizzate.

Ablazione a radiofrequenza

La ablazione a radiofrequenza è una tecnica relativamente nuova che ha dimostrato essere un metodo sufficientemente sicuro di citoriduzione in pazienti con malattia epatica primitiva o secondaria. La sua applicazione al fegato è stata introdotta nel 1990 e la sua prevalenza si è rapidamente diffusa a causa della sua versatilità. La RFA impiega una sonda guidata che distrugge il tumore per ipertermia locale[35].

Anche se la RFA non è intesa a rimpiazzare la resezione epatica, è stata utilizzata come un'alternativa o un'aggiunta alla resezione. Essa ha un ruolo per le pazienti con lesioni più piccole che sono clinicamente inadatte per la resezione epatica, per pazienti con malattia bilobare non resecabile o quale aggiunta alla resezione.

Nonostante l'apparente sicurezza della RFA, sono state descritte **parecchie limitazioni**; la misura delle lesioni o le localizzazioni tumorali centrali prossime ai vasi sanguigni principali appaiono essere un grave determinante per la recidiva locale (tabella 5). Inoltre, la RFA non può essere considerata una modalità curativa come la resezione epatica. Il confronto tra la RFA e la resezione epatica è difficile a causa della mancanza di studi prospettici randomizzati.

Livraghi et al.[26] hanno riportato la loro iniziale esperienza con la RFA percutanea su 24 pazienti con metastasi da carcinoma mammario compreso tra 1 e 6,6 cm. La necrosi completa, visualizzata dalla TC con mezzo di contrasto, è stata ottenuta nel 92% delle lesioni. Nel 58% delle pazienti si sono sviluppate nuove metastasi durante il follow up. Non si è verificata nessuna complicanza maggiore. Ad un follow-up mediano di 19 mesi (4-44 mesi) 10/16 pazienti (63%) con solo metastasi epatiche erano libere da malattia, suggerendo che la RFA è un trattamento efficace per pazienti selezionate con malattia metastatica confinata al fegato. Confrontata con la chirurgia, la RFA offre i vantaggi di essere sicura, relativamente semplice, meno costosa e considerevolmente meno invasiva. Essa ha dimostrato di essere un trattamento efficace con un'alta percentuale di controllo locale, tale da essere considerata una valida alternativa alla resezione in una popolazione selezionata di pazienti. Le differenti percentuali di sopravvivenza ottenute con la RFA confrontate con quelle dopo la chemioterapia o la chirurgia sono dovute alla selezione dei pazienti. Per questa ragione, o a causa del fatto che i gruppi non sono confrontabili, trial comparativi tra l'ablazione, la chemioterapia e la chirurgia nel trattamento delle metastasi epatiche sono impraticabili, oltre che non etici. Inoltre sono necessari studi randomizzati che valutino la RFA in combinazione con la chemioterapia e gli agenti antiangiogenetici, *versus* la chemioterapia da sola, per valutare la risposta globale[27].

Tabella 5. *Ruoli, vantaggi e limitazioni della ablazione a radiofrequenza.*

- Ruoli:
  - lesioni metastatiche più piccole
  - lesioni multifocali, bilobari, non resecabili
  - co-morbilità o insoddisfacente performance status
- Vantaggi (*vs* resezione):
  - basso costo
  - modesta invasività
  - tecnicamente semplice
  - elevata efficacia (alta % di controllo locale)
  - sicurezza (poche complicanze)
  - uso simultaneo o consecutivo di altri trattamenti complementari
- Limitazioni (recidiva in 50-60% casi) nel caso di:
  - lesioni voluminose
  - localizzazione tumorale prossima ai principali vasi sanguigni

Discussione

Il carcinoma della mammella metastatico è generalmente trattato con terapie sistemiche piuttosto che con interventi locali. Attualmente, il trattamento include le terapie sistemiche sulla base della convinzione che la presenza di metastasi epatiche indichi malattia disseminata; ma gli attuali approcci terapeutici non hanno intento curativo. Inoltre, un recente successo con l'ablazione *in situ* e la resezione di tumori epatici secondari hanno condotto a considerare soddisfacente l'uso di queste tecniche in pazienti con metastasi epatiche isolate. Tuttavia, le metastasi da carcinoma mammario limitate al fegato non sono comuni, essendo riportate in solo il 5-12% delle pazienti con malattia metastatica[18]. Alcuni trattamenti locali che includono la perfusione interarteriosa di chemioterapia sono state valutate allo scopo di migliorare la prognosi, ma deve essere ancora stabilita una procedura standard di trattamento. La chemioterapia locale applicata alle pazienti con metastasi del fegato non resecabili ha prodotto risposte solo parziali. I risultati dell'International Breast Cancer Study Group hanno mostrato che la percentuale di risposta alla chemioterapia locale in pazienti che avevano avuto chemioterapia adiuvante dopo il carcinoma mammario non superava il 38%. La sopravvivenza mediana dopo la resezione epatica combinata con la chemioterapia locale era simile alla sopravvivenza dopo resezione epatica da sola (mediana di 15 mesi o 28 mesi). La sopravvivenza stimata a 5 anni non eccedeva il 9%[4].

La resezione epatica dovrebbe essere considerata una delle opzioni per le metastasi isolate, poiché non si è verificata nessuna mortalità chirurgica. Dopo la resezione, la recidiva di metastasi epatiche da carcinoma della mammella è stata rilevata in circa il 56-67% delle pazienti[14]. Gli autori degli studi riportati suggeriscono che la sopravvivenza possa migliorare con l'uso della resezione chirurgica o dell'ablazione di metastasi limitate al fegato **in pazienti selezionate**. Tuttavia, questi studi descrivono solo piccole coorti di pazienti ed i ricercatori hanno notato considerevole eterogeneità nella presentazione e nella progressione della malattia metastatica. Appare utile e logico proporre la resezione o l'ablazione nelle pazienti quando tre condizioni sono confermate: 1) basso rischio operatorio; 2) metastasi epatiche completamente resecabili; 3) assenza di malattia extraepatica (eccetto rare metastasi ossee). I migliori risultati nelle pazienti dopo trattamenti loco-regionali erano associati con buon performance status, lungo intervallo libero da malattia dopo trattamento del tumore primitivo, completa resezione del tumore e limitazione delle metastasi ad un unico sito. Recenti miglioramenti nelle tecniche di imaging hanno reso le metastasi epatiche capaci di essere valutate precocemente e la maggior parte delle pazienti sono seguite routinariamente in follow up con l'ecografia addominale, la risonanza magnetica, a/o la TC. Alcune di queste pazienti sono candidate ad essere selezionate per trattamenti loco-regionali.

I dati da noi riportati indicano che i trattamenti loco-regionali possono determinare sopravvivenze significativamente migliori nelle pazienti con carcinoma della mammella con metastasi epatiche isolate. Tali studi sono obiettivamente difficili da interpretare. Come già accennato, parecchi tipi di errori potrebbero influenzare questi risultati. Non solo il numero di pazienti è troppo esiguo, ma l'arruolamento delle pazienti negli studi clinici è in continuo divenire. Nel caso delle pazienti con carcinoma della mammella in IV stadio, un significativo ostacolo all' arruolamento potrebbe essere il rifiuto del paziente o del medico a considerare una terapia aggressiva in quei casi in cui il carcinoma della mammella metastatico è storicamente considerato una malattia in stadio finale. I dati attuali sollecitano la necessità di trial clinici disegnati allo scopo di determinare l'esatto ruolo della resezione e della RFA in queste pazienti.

Conclusioni e domande aperte

Così come continuano ad evolvere le indicazioni al trattamento del carcinoma alla mammella, egualmente evolve la definizione di quello che costituisce una "cura". Forse stiamo andando verso un tempo in cui il carcinoma della mammella può essere "curato": nel senso che può essere reso innocuo. Potremmo definire "cura" un periodo prolungato di sopravvivenza senza sintomi significativi. Sebbene importanti progressi siano stati fatti nel trattamento multimodale delle pazienti con metastasi epatiche da carcinoma mammario, incluso l'uso di efficaci chemioterapie sistemiche, di terapie ormonali (inibitori dell'aromatasi) e di agenti biologici mitrati (trastuzumab, bevacizumab), lo sviluppo di metastasi a distanza continua ad essere associato ad una cattiva prognosi[26-28].

I dati disponibili in letteratura suggeriscono che i trattamenti loco regionali potrebbero apportare un beneficio significativo in un gruppo selezionato di donne, ma il loro posto nel trattamento multimodale delle metastasi epatiche rimane controverso.

Una chemioterapia selettiva intraarteriosa potrebbe essere valutata per ridurre l'alta incidenza di recidiva epatica dopo resezione. In sintesi, la resezione epatica e l'ablazione a radio frequenza possono essere condotte con minima morbilità e bassa mortalità **in gruppi selezionati di donne** con metastasi epatiche da carcinoma della mammella. Crediamo che la chemioterapia sistemica rappresenti la terapia standard per pazienti con recidiva, ma il tempo di sopravvivenza mediano è stato calcolato in non più di 5-12 mesi[39-43]. Inoltre, come valutato in alcuni studi, quando ogni chemioterapia o terapia ormonale è inefficace per le metastasi epatiche e non c'è malattia extra epatica, l'approccio loco regionale aggressivo può prolungare la sopravvivenza.

Le terapie target[37-38] stanno cambiando il nostro attuale approccio al trattamento del carcinoma alla mammella. Il trastuzumab, un anticorpo monoclonale ricombinante umanizzato che riconosce HER2, è tra i primi farmaci target specifici che sono stati approvati per l'impiego clinico. Il bevacizumab è stato valutato positivamente nel carcinoma della mammella metastatico. I maggiori cambiamenti nello sviluppo clinico delle terapie target con anticorpi monoclonali includono l'appropriata selezione di pazienti, l'identificazione di ottime schedule e la combinazione con i trattamenti convenzionali. L'uso esteso di nuovi e più efficaci agenti chemioterapici combinati con le molecole target e con la chirurgia più sicura ha incoraggiato chirurghi ed oncologi a estendere le indicazione alla resezione epatica. Studi prospettici randomizzati che confrontano i trattamenti convenzionali e quelli target con e senza i trattamenti loco regionali potranno confermare o meno se questi migliorano realmente la sopravvivenza delle pazienti.

Bibliografia

1. Silva Orlando E, Zurrida S, eds. Breast cancer. A practical guide. Third edition New York: Elsevier Saunders 2005.
2. Mack M, Straub R, Eichler K, Söllner O, Lehnert T, Vogl TJ. Breast cancer metastases in liver: laser-induced interstitial thermotherapy- local tumor control rate and survival data. Radiology 2004; 233: 400-9.
3. Molino A, Pavarana M, Guglielmi A: Il ruolo dei trattamenti loco-regionali nella malattia metastatica. Supplemento a International Trends in Oncology 2005; 9: 83-6.
4. Maksan SM, Lehnert T, Bastert, Herfarth C. Curative liver resection for metastatic breast cancer. Eur J of Surg Oncology 2000; 26: 209-12.
5. Bathe OF, Kaklamanos IG, Moffat FL, Boggs J, Franceschi D, Livingstone AS. Metastasectomy as a cytoreductive strategy for treatment of isolated pulmonary and hepatic metastases from breast cancer. Surg Oncol 1999; 8: 35-42.
6. Selzner M, Morse MA, Vredenburgh JJ, Meyers WC, Clavien PA. Liver metastases from breast cancer: long-term survival after curative resection. Surgery 2000; 127: 383-9.
7. Kuvshinoff B, Fong Y. Surgical therapy of liver metastases. Semin Oncol 2007; 34: 177-85.
8. Singletary SE, Walsh G, Vauthey JN, Curley S, Sawaya R, Weber KL, et al. A role for curative surgery in the treatment of selected patients with metastatic breast cancer. Oncologist 2003; 8: 241-51.
9. Sahani DV, Kalva SP. Imaging the liver. Oncologist 2004; 9: 385-97.
10. Elias D, Maisonnette F, Druet-Cabanac M, Ouellet JF, Guinebretiere JM, Spielmann M, et al. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. Am J Surg 2003; 185: 158-64.
11. Pocard M, Pouillart P, Asselain B, Falcou MC, Salmon RJ. Hepatic resection for breast cancer metastases: results and prognosis (65 cases). Ann Chir 2001; 126: 413-20.
12. Adam R, Aloia T, Krissat J, Bralet MP, Paule B, Giacchetti S, et al. Is liver resection justified for patients with hepatic metastases from breast cancer? Annals of Surgery 2006; 244: 897-908.

13. Adam R, Salmon R, Elias D, et al. Breast cancer liver metastases: What way be the role of surgery combined with chemotherapy? Journal of Clinical Oncol 2007; 41: 1039.
14. Sakamoto Y, Yamamoto J, Yoshimoto M, Kasumi F, Kosuge T, Kokudo N, et al. Hepatic resection for metastatic breast cancer: prognostic analysis of 34 patients. World J Surg 2006; 29: 524-7.
15. Tholen A, Benckert C, Jonas S, Lopez-Hänninen E, Schnoll J, Neumann U, et al. Liver resection for metastases from breast cancer. J Surg Oncol 2008; 97: 25-9.
16. Er O, Frye DK, Kau SW, Broglio K, Valero V, Hortobagyi GN, et al. Clinical course of breast cancer patients with metastases limited to the liver treated with chemotherapy. Cancer J 2008; 14: 62-8.
17. Raab R, Nussbaum KT, Behrend M, Weimann A. Liver metastases of breast cancer: results of liver resection. Anticancer Res 1998; 18: 2231-4.
18. Raab R, Nussbaum KT, Werner U, Pichlmayr R. Liver metastases in breast carcinoma. Results of partial liver resection. Chirurg 1996; 67: 234-7.
19. Yoshimoto M, Tada T, Saito M, Takahashi K, Uchida Y, Kasumi F. Surgical treatment of hepatic metastases from breast cancer. Breast Cancer Res Treat 2000; 59: 177-84.
20. Pocard M, Falcou MC, Salmon RJ. On the prognosis criteria for hepatic resection in cases of breast metastases. Surgery 2001; 129: 651-2.
21. Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. Breast Cancer Res Treat 1999; 56: 67-78.
22. Clark GM, Sledge GW Jr, Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. J Clin Oncol 1987; 5: 55-61.
23. Vlastos G, Smith DL, Singletary SE, Mirza NQ, Tuttle TM, Popat RJ, et al. Long-term survival after an aggressive surgical approach in patients with breast cancer hepatic metastases. Ann Surg Oncol 2004; 11: 869-74.
24. Schneebaum S, Walker MJ, Young D, Farrar WV, Minton JP. The regional treatment of liver metastases from breast cancer. J Surg Oncol 1994; 55: 26-32.
25. Bleicher RJ, Allegra DP, Nora DT, Wood TF, Feshaq LJ, Blichfk AJ. Radiofrequency ablation in 447 complex unresectable liver tumors: lessons learned. Ann of Surg Oncol 2002; 10: 52-8.
26. Livraghi T, Goldberg N, Solbiati L, Meloni F, Ierace T, Gazelle GS. Percutaneous radio-frequency ablation of liver metastases from breast cancer: initial experience in 24 patients. Radiology 2001; 220: 145-9.
27. Pereira PL. Actual role of radiofrequency ablation of liver metastases. Eur Radiol 2007; 17: 2062-70.
28. Scaife CL, Curley SA. Complication, local recurrence, and survival rates after radiofrequency ablation for hepatic malignancies. Surg Oncol Clin N Am 2003; 12: 243-55.
29. Lencioni R, Goletti O, Armillotta N. Radio-frequency thermal ablation of liver metastases with cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol 1998; 8: 1205-11.
30. Rossi S, Buscarini E, Garbagnati F, Di Stasi M, Quaretti P, Rago M, et al. Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. AJR Am J Roentgenol 1998; 170: 1015-22.
31. Solbiati G, Ierace T, Goldberg SN. Hepatic metastases: percutaneous radio-frequency ablation with cooled-tip electrode. Radiology 1997; 205: 367-73.
32. van Duijnhoven FH, Jansen MC, Junggeburt JM, van Hillegersberg R, Rijken AM, van Coevorden F, et al. Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. Ann Surg Oncol 2006; 13: 651-8.
33. Kuvshinoff BW, Ota DM: Radiofrequency ablation of liver tumors: influence of technique and tumor size. Surgery 2002; 132: 605-11.
34. Kornprat P, Jarnagin WR, Gonen M, De Matteo RP, Fong Y, Blumgart LH, et al. Outcome after hepatectomy for multiple (four or more) colorectal metastases in the era of effective chemotherapy. Ann Surg Oncol 2007; 14: 1151-60.
35. Garrean S, Hering J, Scott Helton W, Espat NJ. A primer on transarterial, chemical, and thermal ablative therapies for hepatic tumors. Am J Surg 2007; 194: 79-88.
36. Biasco G, Derenzini E, Grazi G, Ercolani G, Ravaioli M, Pantaleo MA, et al. Treatment of hepatic metastases from colorectal cancer: many doubts, some certainties. Cancer Treat Rev 2006; 32: 214-8.
37. Mollica S, De Vita VT Jr, Hellman S. Targeted therapies: anticerpé monoclonali. International Trends in Oncology 2005; 3: 68-73,
38. Gasparini G, Longo R, Torino F, Morabito A. Therapy of breast cancer with molecular targeting agents. Ann Oncol 2005; 16: 28-36.
39. O'Shaughnessy J. Extending survival with chemotherapy in metastic breast cancer. Oncol 2005; 10: 20-9.
40. Bruzzi P, Del Mastro L, Sormani MP, Bastholt L, Danova M, Focan C, et al. Objective response to chemotherapy as a potential surrogate end point of survival in metastatic breast cancer. J Clin Oncol 2006; 23: 5117-25.
41. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. Oncologist 2003; 8: 14-20.
42. Pumoleau P. Treatment of patients with liver metastases. Anti-Cancer Drugs 1996; 7 (suppl 2): 21-3.
43. Atalay G, Biganzoli L, Renard F, Paridaens R, Cufer T, Coleman R, et al. Clinical outcome of breast cancer patients with liver metastases in the anthracycline-taxane era. Breast Cancer Res Treat 2002; 76 (suppl 1): S47.
44. Lernite E, Marzano E, Chéreau E, Ronzier R, Pessaux P. Surgical resection of liver metastases from breast cancer. Surg Oncol 2009; July 8 [Epub ahead of print].
45. Diamond JR, Finlayson CA, Borges VF. Hepatic complication of breast cancer. Lancet Oncol 2009; 10: 615-21.
46. Vogl TJ, Naguib NN, Nour-Eldin, Eichler K, Zangos S, Gruber-Rouh T. Transarterial chemoembolization (TACE) with mitomycin C and pemetabine for liver metastases in breast cancer. Eur Radiol 2009; August 6 [Epub ahead of print].

Indirizzo per la corrispondenza:
Dott. Cristina Raimondi
Azienda Ospedaliera Universitaria P. Giaccone
Oncologia Medica
Via del Vespro 129
90127 Palermo
E-mail: raimondicristina@tiscali.it

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Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer
A randomized phase II SICOG trial

Pasquale Comella[a,*], Vincenzo E. Chiuri[b], Giuseppe De Cataldis[c], Gianfranco Filippelli[d], Luigi Maiorino[e], Giacomo Vessia[f], Riccardo Cioffi[g], Sergio Mancarella[h], Carlo Putzu[i], Ettore Greco[j], Laura Palmeri[k], Raffaele Costanzo[a], Antonio Avallone[a], Luca Franco[a]

[a] National Tumour Institute, Via Semmola, 80131 Naples, Italy
[b] Vito Fazi Hospital, Piazza Muratore 1, 73100 Lecce, Italy
[c] De Procida Hospital, Via Colenda, 84100 Salerno, Italy
[d] San Francesco di Paola Hospital, Via Provinciale, 87027 Paola, Italy
[e] San Gennaro Hospital, Via S. Gennaro dei Poveri 5, 80131 Naples, Italy
[f] Umberto I Hospital, Viale Margherita, 70022 Altamura, Italy
[g] San Sebastiano Hospital, Via Palasciano, 81100 Caserta, Italy
[h] Santa Caterina Hospital, Via Roma, 73013 Galatina, Italy
[i] University School of Medicine, Via S. Pietro 8, 07100 Sassari, Italy
[j] City Hospital, Via Perugini, 88046 Lamezia Terme, Italy
[k] University School of Medicine, Via Vespro 27, 6100 Palermo, Italy

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ABSTRACT

Purpose: To estimate the safety, activity, and impact on quality of life of a combination of gemcitabine and pemetrexed in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) in the context of a randomized two-stage phase II study.
Patients and methods: Patients in stage IIIB or IV NSCLC were randomly allocated to receive either gemcitabine 1250 mg/m² on day 1, and pemetrexed (Alimta) 500 mg/m² followed by gemcitabine 1250 mg/m² on day 8 of a 3-weekly cycle (GA arm), or paclitaxel 120 mg/m² followed by gemcitabine 1000 mg/m², both given on days 1 and 8 of a 3-weekly cycle (PG arm).
Results: 105 (GA arm, 51; PG arm, 54) eligible patients (stage IV, 32 and 30, respectively) were enrolled into this study; thereafter, accrual was stopped due to first-stage analysis. The response rate was 20% (95% confidence interval [CI], 10–33%) in the GA arm, and 32% (95% CI, 20–46%) in the PG arm. Median progression-free survival was 5.1 (95% CI, 3.7–6.5) months in the GA arm, and 8.3 (95% CI, 5.9–10.7) months in the PG arm, while median overall survival was 10.5 (95% CI 7.1–13.9), and 13.3 (95% CI 11.7–14.9) months, respectively. Severe neutropenia (36% vs 22%), and febrile neutropenia (14% vs 7%) were more common with the GA regimen, while hair loss (52% vs 16%) and any grade peripheral neuropathy (31% vs 2%) occurred more frequently with PG regimen. Other severe side effects of GA regimen were diarrhoea (10%), liver enzyme derangement (10%), and fatigue (8%).
Conclusion: The GA regimen was tolerated and moderately active in advanced or metastatic NSCLC. However, this combination did not yield any advantage in comparison with the PG regimen, and does not deserve further evaluation.

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1. Introduction

Despite the clinical introduction during the last decade of novel active cytotoxic drugs such as paclitaxel (PTX), gemcitabine (GEM), docetaxel (DTX), and vinorelbine (VNR) for the treatment of non-small cell lung cancer (NSCLC), the prognosis of patients with a locally advanced or metastatic disease remains poor. A combination of cisplatin (CDDP) or carboplatin (CBDCA) with one of these novel compounds (platinum-based doublets) still represents the standard of care for these patients. Indeed, in the ECOG randomized trial (E1594) comparing four platinum-based doublets (CDDP + PTX, CDDP + GEM, CDDP + DTX, or CBDCA + PTX), the overall survival (OS) of patients did not differ significantly, the only observed differences being in side effects of these regimens [1]. Similar findings were

* Corresponding author. Tel.: +39 0815903227; fax: +39 0815903726.
E-mail address: pasqualecomella@libero.it (P. Comella).

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seen in an Italian study, in which three platinum-based doublets (CDDP + VNR, CDDP + GEM and CBDCA + PTX) were compared. Also in this study, haematologic and some non-haematologic side effects differed according to the combination utilised [2].

Several investigators have also assessed platinum-free doublets, in order to avoid the nephrotoxicity and neurotoxicity of CDDP, and the bone marrow toxicity of CBDCA. Indeed, CDDP- or CBDCA-based doublets were challenged by doublets including GEM with VNR or a taxane (either PTX or DTX) [3–9]. No significant difference in patients outcome were reported, while these regimens differed in some peculiar side effects.

To extrapolate the role of CDDP, the Southern Italy Cooperative Oncology Group (SICOG) randomly compared two triplets including CDDP with their corresponding CDDP-free doublets. Actually, addition of CDDP did increase the occurrence of haematologic and some non-haematologic side effects, with no significant improvement of PFS or OS [10]. Moreover, the GEM + PTX combination was proven similarly safe and active in young as well in elderly patients [11]. In addition, a meta-analysis of trials comparing platinum-including and platinum-free doublets did not show a better OS when platinum-including regimens were compared with third-generation platinum-free combinations [12].

Pemetrexed is a novel folate-based anticancer compound active against NSCLC. The recommended dosage as single-agent treatment is 500 mg/m^2, associated with vitamin (folic acid and B_{12}) supplementation [13,14]. Pemetrexed has been randomly compared with docetaxel in the second-line treatment of patients with NSCLC. In this study, pemetrexed produced non-inferior efficacy outcomes, but fewer side effects, than docetaxel [14]. Pemetrexed has also shown interesting activity when used in first-line [15,16], and some phase II trials have been carried-out on the combination of pemetrexed plus CDDP, CBDCA, or oxaliplatin. Response rate ranged from 24% to 45%, while median PFS and OS ranged from 4.5 to 6.3 months, and from 8.9 to 10.9 months, respectively [17–19]. On this background, the combination of CDDP and pemetrexed has been compared with CDDP and GEM in a phase III trial. This study demonstrated the non-inferiority of CDDP and pemetrexed in terms of PFS and OS. Moreover, haematologic toxicity was quite lower with this regimen [20]. Noteworthy, pemetrexed resulted more effective in terms of PFS and OS in patients with non-squamous histology, either when used alone in second-line [14], and in combination with CDDP in first-line [20]. Conversely, it produced worse results than the comparator treatment in either studies in squamous cell carcinoma [21].

The combination of pemetrexed and GEM seems particularly attractive for treating NSCLC patients, considering low toxicity profile of each compound. Some phase II trials have explored the safety and activity of this combination, with conflicting results. Indeed, Monnerrat et al. treated 60 patients with GEM 1250 mg/m^2 on day 1 and 8, and pemetrexed 500 mg/m^2 on day 8 (after GEM infusion), recycling every 3 weeks. A partial response was reported in 15.5% of patients. Median PFS was 5.0 months, and median OS was 10.1 months. Grade 3 and 4 side effects were neutropenia (62%), febrile neutropenia (17%), fatigue (23%), and elevation of aspartate aminotransferase (15%) [22]. Ma and Nair conducted a phase II randomized trial, in which three schedules of the combination of GEM 1250 mg/m^2 and pemetrexed 500 mg/m^2, recycled every 3 weeks, were tested: in schedule A, pemetrexed was given on day 1, followed by GEM on days 1 and 8; in schedule B, GEM preceded pemetrexed on day 1, and it was repeated on day 8; in schedule C, GEM was given on days 1 and 8, and pemetrexed on day 8 (before GEM). Schedule B was closed at interim analysis for inferior efficacy. Response rate was 31% with schedule A and 16% with schedule C. However, median PFS (4.7 *vs* 4.4 months), as well as OS (11.4 *vs* 11.8 months) were similar. Schedule A seemed less toxic compared with schedule C (grade ≥3 adverse events: 86% *vs* 94%) [23]. The same schedule B of the previous trial was also assessed by Treat et al. in 53 patients: these investigators reported a 33% RR, a PFS of 3.3 months, and an OS of 10.3 months. Neutropenia (43%) and dyspnoea (15%) were the most frequent severe adverse events [24]. On the contrary, West et al. reported on a series of 54 patients treated with the schedule C, but with pemetrexed following GEM on day 8. Thirteen percent of patients achieved a partial response, but severe toxicity was relevant: they reported neutropenia (40%), febrile neutropenia (11%), thrombocytopenia (11%), fatigue (21%), and dyspnoea (21%) [25]. Finally, a biweekly regimen of pemetrexed 500 mg/m^2 and GEM 1500 mg/m^2 was assessed in 45 elderly or poor performance status (PS) patients by Blakeley et al. [26]. While no activity was seen in patients with a PS of 2, these investigators reported a 25% RR in patients with PS 0–1, with a corresponding median PFS of 3.8 months. On the whole, 49% of patients had a grade 3 or higher drug-related adverse event.

On this background, we deemed interesting to further investigate the safety and activity, as well as the impact on the quality of life, of a combination of GEM and pemetrexed in advanced NSCLC patients in the context of a randomized trial. Based on our previous experience, we selected as reference regimen for the present study the combination of GEM and PTX.

2. Patients and methods

2.1. Entry criteria

Eligible for this study were patients affected by NSCLC in stage IIIB or IV, aged ≥18 years, unexposed to previous adjuvant or palliative chemotherapy, ECOG PS ≤1, Charlson comorbidity score ≤2, normal bone marrow, renal and liver function, at least one measurable lesion, and no brain metastases. Main exclusion criteria were: active and uncontrolled metabolic disease or infection, severe cardiac arrhythmias, previous or concurrent malignancies. Patients gave their informed consent to participate into this study, which was approved by the Independent Ethics Committee of the National Tumour Institute of Naples.

2.2. Pretreatment evaluation

Baseline work-up included a complete history and physical examination, ECG, chest X-ray, respiratory tests, fiberoptic broncoscopy, and brain, chest and upper abdomen computed tomography (CT) scan. Radionuclide bone scan was also performed in the case of clinically suspected lesions. Complete blood cell count with white blood cell differential and platelet count, full chemistry profile, urinalysis, and determination of serum level of CEA, Cyfra 21.1, and NSE, were performed within 2 weeks before enrolment. Quality of life was measured through the EORTC questionnaires QLQ-C30 and QLQ-LC13, filled in by patients before randomization.

2.3. Treatment

Patients were centrally registered and, after stratification according to Centre and stage of disease (IIIB *vs* IV), were randomly allocated to receive either GEM 1250 mg/m^2 (as 1 h i.v. infusion) on day 1, pemetrexed (Alimta) 500 mg/m^2 (as 10 min i.v. infusion) followed by GEM 1250 mg/m^2 (as 1 h i.v. infusion) on day 8 of a 3-weekly cycle (GA arm); or PTX 120 mg/m^2 (as 1 h i.v. infusion) followed by GEM 1000 mg/m^2 (as 1 h i.v. infusion), both given on days 1 and 8 of a 3-weekly cycle (PG arm).

Dexamethazone 4 mg i.v., ranitidine 50 mg i.v. and prometh azine 50 mg i.m. were delivered before each drugs administration in both arms. In the GA arm, patients started to take folic acid 350–1000 μg orally on day 1. This dosage was continued until 3 weeks after the last dose of pemetrexed. An i.m. injection of vitamin B_{12} 1000 μg

was administered on day 1, and repeated approximately every 9 weeks.

Treatment was planned for a minimum of 3 cycles, and up to a maximum of 6 cycles. Recycling was permitted after full recovery of side effects from previous cycle, otherwise a 1-week delay was allowed. On day 8, doses were reduced by 25% for a grade 1 neutropenia or thrombocytopenia, while treatment was omitted in the presence of a greater toxicity.

2.4. Assessment of toxicity, response, and quality of life

During treatment, a blood cell count with differential was performed weekly, while biochemistry was repeated at every cycle. Non-haematologic side effects of previous cycle were assessed at the time of recycling. Toxicity was scored according to the WHO classification [27], and the worst toxicity encountered during the whole treatment by each patient was recorded.

After 3 cycles, all initially abnormal procedures were repeated for assessing tumour response according to the RECIST criteria [28]. Accordingly, responses had to be confirmed after a minimum of 4-week interval. All eligible patients were included in the analysis of response on an intent-to-treat basis. Discontinuation of treatment due to any cause was considered as a treatment failure, and included into the denominator of the response rate.

Changes in symptoms and global health status/quality of life were assessed by asking patients to fill in again, before the evaluation of response, both the EORTC questionnaires.

2.5. Statistical design

The primary aim of this study was to assess the response rate (RR) and the acute toxicity of GEM and pemetrexed combination. To define the sample size, a Simon two-stage optimal design was adopted [29]. Assuming a 30% response rate as the minimum activity of interest, to have an 80% power to demonstrate (with an alpha error = 0.05) an alternative hypothesis of a 45% response rate, at least 17 responses among the first 46 patients, and at least 25 responses among a total of 65 patients were required. RRs were calculated with their exact 95% confidence intervals (CI).

PFS was measured from the date of randomization to the date of occurrence of tumour progression, or death. Patients withdrawn from treatment for reasons other than progression were considered as censored at the date of last cycle. OS was measured from the date of randomization to the date of death, or last follow-up. PFS and OS probabilities, with their 95% CI, were estimated by the Kaplan–Meier method [30]. Comparisons were made using the Cox analysis [31], and expressed as hazard ratio (HR), with its 95% CI. Baseline scores of single items and domains of the quality of life in the two arms of the study were compared by the Mann–Whitney test. Differences from baseline scores after 3 cycles of treatments were compared by the Wilcoxon rank sum test.

3. Results

3.1. Patients accrual

From May 2006 to October 2007, 108 patients were enrolled into this study by 11 SICOG centres, but three patients (two patients in the GA arm, and one patient in the PG arm) withdraw their consent, and did not receive the assigned regimen. Accrual was stopped after the assessment of response among the patients entered into the first-stage of the study, because the number of confirmed responses was inferior to that required by the statistical design. Main demographic and clinical characteristics of patients were well balanced between the two arms of treatment, as shown in Table 1. Most patients (41%) were affected by adenocarcinoma, and 59% of them had a metastatic disease.

Table 1
Main demographic and clinical characteristics according to regimens on study.

Characteristics	PG regimen		GA regimen	
	No.	%	No.	%
Eligible patients	54	100	51	100
Males	46	85	40	78
Females	8	15	11	22
Median age (range) years	64 (44–77)		66 (40–76)	
Aged > 70 years	14	26	12	24
Charlson score 0	26	48	23	45
Charlson score 1	19	35	20	39
Charlson score 2	9	17	8	17
Squamous cell carcinoma	21	39	18	35
Adenocarcinoma	24	44	19	37
Large cell/undifferentiated	1	2	2	4
Unclassified	8	15	12	24
Recurrent disease	5	9	2	4
Stage IIIB dry	14	26	14	27
Stage IIIB wet	10	18	5	10
Stage IV	30	56	32	63
Performance status 0	15	28	12	24
Performance status 1	39	72	39	76
Weight loss > 5%	10	19	13	26

3.2. Treatment disposition

As reported in Table 2, a median of 4 cycles were delivered in the GA arm, as opposed to 5 cycles in the PG arm. Similar proportions of patients in the two arms received four or 6 cycles of treatment. In the GA arm, 9% of doses were reduced, and 1% were omitted. In the PG arm, 14% of doses were reduced, and 2% were omitted.

3.3. Activity

In the GA arm, 15 (confirmed, 10) partial responses were registered, for a RR of 20% (95% CI, 10–33%). In the PG arm, 21 patients achieved a partial response, which was confirmed in 17 cases. Therefore, the RR was 32% (95% CI, 20–46%). Comparable proportions of patients achieved a stable disease or showed progression during treatment, while a greater number of patients in the GA arm were not assessed for response because of early clinical deterioration (Table 3).

Among metastatic patients, confirmed RR was 22% in the GA arm, and 27% in the PG arm. Similarly, activity of GA regimen was inferior to the PG regimen either in adenocarcinomas (26% vs 38%), and in squamous cell carcinomas (22% vs 33%).

3.4. Toxicity

Acute toxicity of the two regimens is reported in Table 3. The most common severe haematologic toxicity of the GA regimen was neutropenia (36%), and febrile neutropenia (14%). Liver enzymes derangement (10%), diarrhoea (10%), and fatigue (8%) were the

Table 2
Treatment disposition according to regimens on study.

Treatment disposition	PG regimen		GA regimen	
	No.	%	No.	%
Delivered cycles	228		108	
Median number of cycles/patient range	5, 1–6		4, 1–6	
Patients treated with				
≥2 cycles	50	93	44	86
≥4 cycles	31	57	26	51
6 cycles	18	33	17	33

Table 3
Acute toxicity according to regimen on study.

WHO toxicity grade	PG regimen				GA regimen			
	Any	%	3–4	%	Any	%	3–4	%
Neutropenia	30	56	12	22	34	67	18	35
Febrile neutropenia	–	–	4	7	–	–	7	14
Thrombocytopenia	15	28	4	7	16	32	2	4
Anaemia	26	48	3	6	28	56	3	6
Nausea/vomiting	22	41	3	6	24	48	2	4
Renal toxicity	2	4	0	0	1	2	0	0
Neurotoxicity	17	31	2	4	1	2	0	0
Stomatitis	12	22	0	0	10	20	0	0
Hair loss	28	53	12	22	8	16	2	4
Liver toxicity	23	39	4	7	24	48	5	10
Diarrhoea	15	28	3	6	13	26	5	10
Skin toxicity	6	11	0	0	10	20	0	0
Fatigue	23	39	4	7	20	40	4	8
Myalgia	4	7	0	0	2	4	0	0

most frequent non-haematologic severe side effects. With the PG regimen, neutropenia was less pronounced, but any grade neurotoxicity (31%), and alopecia (52%) were significantly ($P=0.001$) more frequent than with the GA regimen. Conversely, the GA regimen produced more skin toxicity of any grade.

3.5. Quality of life

Baseline quality of life questionnaires were available for 100 of 105 patients: 47 (92%) patients in the GA arm, and 53 (98%) patients in the PG arm. Excluding a non-significantly greater pain score registered in the GA arm (median, 33 *vs* 17), no other differences were noted as regards to the baseline single item or domain scores. The median global health status/quality of life score was 67 (range, 17–100) in the GA arm, and 58 (range, 0–100) in the PG arm.

After three courses, questionnaires were available for 29 (57%) patients in the GA arm, and for 37 (69%) patients in the PG arm. Excluding a significantly ($P< 0.001$) worse score for the subjective perception of peripheral neuropathy and hair loss in the PG arm, no other different changes from baseline values were registered in the two arms of the study at this time point.

3.6. Post-study treatment

Five patients in both arms, showing stable disease after three courses, were submitted to thoracic radiotherapy. In the GA arm, second-line chemotherapy consisted of docetaxel, alone (eight cases) or combined with CDDP or CBCDA (two cases), or PTX plus GEM (one case). Eight patients received erlotinib in second (four cases), or third line (four cases). In the PG arm, seven patients received second-line pemetrexed, alone (six cases), or with CBDCA (one case), and four received docetaxel with CDDP. Eight patients were treated with erlotinib.

3.7. PFS and OS analysis

As of February 2009, after a median potential follow-up of 22 (range, 14–33) months, 88 (84%) patients progressed, and 78 (74%) eventually died. The PFS curves are plotted in Fig. 1. Median PFS was 5.1 (95% CI, 3.7–6.5) months in the GA arm, and 8.3 (95% CI, 5.9–10.7) months for the PG arm (HR, 1.48 [95% CI, 1.20–1.67], $P= 0.004$). Fig. 2 shows the OS curves: 1-year survival probability was 42% in the GA arm, and 59% in the PG arm: 2-year survival probability was 23% for PG arm, while no patient survived beyond 2 years in the GA arm. Median OS was 10.5 (95% CI, 7.1–13.9) months for GA arm, and 13.3 (95% CI, 11.7–14.9) months for PG arm [HR, 1.39 [95% CI, 1.04–1.61], $P= 0.036$]. A similar difference in favour of PG treatment was observed comparing OS of patients with non-squamous histology. Conversely, OS for metastatic patients was similar in the two arms: median, 9.1 (95%CI, 4.5–14.7) *vs* 9.4 (95% CI, 5.6–13.2) months, respectively.

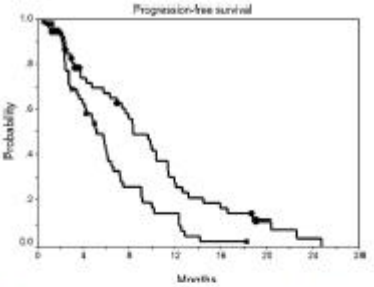

Fig. 1. Estimated progression-free survival probabilities according to the regimens on study (circles, PG regimen; squares, GA regimen).

4. Discussion

The results of this study clearly showed that the combination of GEM and pemetrexed is safe but only moderately active in advanced or metastatic NSCLC patients. Indeed, the actual number of confirmed partial responses (10 out of 51 patients) was inferior to that required by the statistical design for continuing patients accrual, and considering the 95% CI (20–33%) of the RR obtained in our study, we can rule-out that this regimen may produce a major response in more than one-third of treated patients. In addition, although the random assignment of patients was carried-out only for excluding a selection bias [29], and was not aimed at comparing the two regimens, we have to underline that the GA was inferior in any end-point compared with the PG treatment. Indeed, RR was lower either in the whole population (20% *vs* 32%), and among metastatic patients (22% *vs* 27%). This lower activity translated in a poorer PFS (median, 5.1 *vs* 8.3 months). OS was also shorter (median, 10.5 *vs* 13.3 months) for patients treated with GA than with PG combination, despite a similar administration of salvage treatments.

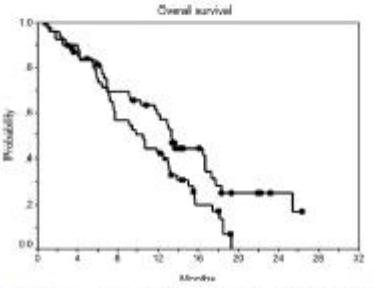

Fig. 2. Estimated overall survival probabilities according to the regimens on study (circles, PG regimen; squares, GA regimen).

As regards to the tolerability of the GA regimen, severe neutropenia (36%), and febrile neutropenia (14%) were the main hematologic side effects of this treatment. In our hands, occurrence of neutropenia was slightly lower than that observed in other phase II studies using the same schedule (ranging from 40% to 69%) [21–24], but frequency of febrile neutropenia was close to the highest rate even reported by others (ranging from 5% to 15%). The haematologic as well as the non-haematologic toxicity of the GA regimen was manageable. Conversely, the PG regimen produced more alopecia and peripheral neuropathy. Actually, a significant difference in quality of life between the PG and GA arm after 3 cycles was just found for these two items.

In conclusion, the GA regimen was moderately active in advanced NSCLC, and it did not show any advantage in terms of RR, PFS, and OS in comparison with the PG regimen. Therefore, in our opinion the GA combination does not deserve further investigation in this disease. On the other hand, the PG regimen was confirmed as an appealing platinum-free option for treating NSCLC patients, regardless of their age.

Conflict of interest

None.

Acknowledgments

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References

[1] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advance non-small cell lung cancer. NEJM 2002;346:92–8.
[2] Scagliotti GV, De Marinis F, Rinaldi M, Crinò L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small cell lung cancer. J Clin Oncol 2002;20:4285–91.
[3] Smit EF, van Meerbeeck JPAM, Lianes P, Debruyne C, Legrand C, Schramel F, et al. Three-arm randomized study of two cisplatinum-based regimens and paclitaxel plus gemcitabine in advanced non-small cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer. J Clin Oncol 2003;21:3909–17.
[4] Kosmidis P, Mylonakis N, Nicolaides C, Kalofonos C, Samantas E, Boukovinas J, et al. Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small cell lung cancer: a phase III randomized trial. J Clin Oncol 2002;20:2578–85.
[5] Kosmidis PA, Kalofonos HP, Christodoulou C, Syrigos K, Makatsoris T, Skarlos D, et al. Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small-cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. Ann Oncol 2008;19:115–22.
[6] Georgoulias V, Ardavanis A, Tsiafaki X, Agelidou A, Mavroudoulou F, Anagnostopoulou O, et al. Vinorelbine plus cisplatin versus docetaxel gemcitabine advanced non-small cell lung cancer. A phase III randomized trial. J Clin Oncol 2005;23:2637–45.
[7] Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, et al. Platinum-based and non-platinum-based chemotherapy in advanced non-small cell lung cancer: a randomised multicentre trial. Lancet 2001;357:1478–84.
[8] Pujol J-L, Breton J-L, Gervais R, Rebischa F, Depierre A, Moreau JF, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602–10.
[9] Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF, et al. Gemcitabine plus vinorelbine versus cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small cell lung cancer: a phase III trial of the Italian GEMVIN investigators and the National Cancer Institute of Canada Clinical Trial Group. J Clin Oncol 2003;21:3025–34.
[10] Cornella P, Filippelli G, De Cataldis G, Mansidda B, Franci G, Maiorino L, et al. Efficacy of the combination of cisplatin with either gemcitabine and vinorelbine or gemcitabine and paclitaxel in the treatment of locally advanced or metastatic non-small-cell lung cancer: a phase III randomized trial of the Southern Italy Cooperative Oncology Group (SICOG 0101). Ann Oncol 2007;18:324–30.
[11] Cornella P, Gamhardella A, Franci G, Avallone A, Costanzo R. Comparison of the safety and efficacy of paclitaxel plus gemcitabine combination in young and elderly patients with locally advanced or metastatic non-small cell lung cancer. A retrospective analysis of the Southern Italy Cooperative Oncology Group trials. Crit Rev Oncol Hematol 2008;65:164–71.
[12] D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small cell lung cancer. A meta-analysis of published literature. J Clin Oncol 2005;23:2926–36.
[13] Adjei AA. Pemetrexed (Alimta), a novel multitarget antineoplastic agent. Clin Cancer Res 2004;10:4297S–805.
[14] Hanna N, Shepherd FA, Fossella SV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589–97.
[15] Clarke S, Boyer M, Milward M, Boyer MJ, Millward MJ, Ackland SP. Phase II study of pemetrexed disodium (ALIMTA, LY231514), in chemonaive patients with advanced non-small cell lung cancer. Ann Oncol 2002;13:737–41.
[16] Rusthoven J, Eisenhauer E, Butts C, Gregg R, Dancey J, Huber B, et al. Multitarget antifolate of LY231514 as first-line chemotherapy for patients with advanced non-small cell lung cancer: a phase II study-National Institute of Canada Clinical Trial Group. J Clin Oncol 1666; 17: 1764–0.
[17] Shepherd FA, Dancey J, Arnold A, Neville A, Rusthoven J, Johnson RD, et al. Phase II study of pemetrexed disodium, a multitarget antifolate, and cisplatin as first-line therapy in patients with advanced non-small cell lung carcinoma: a study of the National Institute of Canada Clinical Trials Group. Cancer 2001;92:595–600.
[18] Scagliotti GV, Kortsik C, Dark GG, Price A, Manegold C, Rosell R, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter randomized phase III trial. Clin Cancer Res 2005;11:690–6.
[19] Zinner RG, Fossella FV, Gladish GW, Glisson BS, Blumenschein Jr GR, Papadimitrakopoulou VA, et al. Phase II of pemetrexed in combination with carboplatin in first-line treatment of advanced non-small cell lung cancer. Cancer 2005;104:2448–56.
[20] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.
[21] Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist 2009;14:000–10.
[22] Monnerat C, Le Chevalier T, Kelly K, Otunuju CK, Brahmer J, Novello S, et al. Phase II study of pemetrexed-gemcitabine combination in patients with advanced-stage non-small cell lung cancer. Clin Cancer Res 2004;10:5409–46.
[23] Ma CX, Nair S, Thomas S, Mandrekar SJ, Nikcevich DA, Rowland KM, et al. Randomized phase II trial of three schedules of pemetrexed and gemcitabine as front-line therapy for advanced non-small cell lung cancer. J Clin Oncol 2005;23:5029–37.
[24] Treat J, Bonomi P, McCleod M, Christiansen NP, Mintzer DM, Monberg MJ, et al. Administration of pemetrexed immediately following gemcitabine ad front-line therapy in advanced non-small cell lung cancer: a phase II trial. Lung Cancer 2006;53:77–83.
[25] West H, Wakelee HA, Perry MC, Belt RJ, Chen R, Otunajuet C. Gemcitabine and pemetrexed administered in rapid sequence as front-line chemotherapy for advanced non-small-cell lung cancer: a phase II clinical trial. Ann Oncol 2009;20:850–6.
[26] Blakely LJ, Schwartzberg L, Kraton M, et al. A phase II trial of pemetrexed and gemcitabine as first line therapy for poor performance status and/or elderly patients with stage IIIB/IV non-small cell lung cancer. Lung Cancer 2009; doi: 10.1016/j.lungcan.2008.12.017.
[27] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.
[28] Therasse P, Arbuck SG, Eisenhauer EH, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
[29] Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1985;69:1375–81.
[30] Kaplan ES, Meier P. Non parametric estimation for incomplete observations. J Am Stat Assoc 1958;53:557–80.
[31] Cox DR. Regression models and life tables. J R Stat Soc 1972;34:187–202.

Gmail by Google

Laura Palmeri <laura.palmeri@gmail.com>

Casi clinici in oncologia

1 messaggio

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CARCINOSI PERITONEALE DA NEOPLASIA A SEDE PRIMITIVA SCONOSCIUTA CON DIFFERENZIAZIONE NEUROENDOCRINA: SOPRAVVIVENZA A LUNGO TERMINE E RUOLO DEGLI ANALOGHI DELLA SOMATOSTATINA

Laura Palmeri, Sergio Rizzo
Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo - Via del Vespro, 129 - 90127 Palermo- - E-mail: laura.palmeri@gmail.com

IL PAZIENTE

Paziente di sesso maschile, 63 anni all'epoca della prima diagnosi (giugno 2005).
In anamnesi cirrosi epatica HBV correlata, nota dal 2004 (score di Child-Pugh A). Tra la fine del 2004 e i primi mesi del 2005 si ricoverava ripetutamente c/o altro presidio ospedaliero in reparto di nefrologia, per sindrome nefrosica in stadio III, correlata all'infezione da HBV. Nel mese di febbraio ricorreva all'ospedalizzazione, in reparto di nefrologia, per stato anasarcatico, risoltosi con opportuna terapia diuretica. Durante i successivi controlli, a causa del permanere di ascite refrattaria, eseguiva TC torace-addome ± mdc che metteva in evidenza la presenza di carcinosi peritoneale, in assenza di una primitività chiaramente evidenziabile.
Giungeva alla nostra osservazione nel giugno 2005, inviato, per competenza, dallo specialista nefrologo.

L'ESAME OBIETTIVO

All'atto del ricovero il paziente si mostrava in discrete condizioni cliniche generali, PS ECOG 1.
L'obiettività dei principali organi ed apparati, inclusa l'EDAR, risultava negativa, fatta eccezione per la presenza di versamento ascitico di lieve entità; non si repertava nessuna linfoadenomegalia degna di nota nelle sedi clinicamente esplorabili.

GLI ESAMI DI LABORATORIO E LE INDAGINI STRUMENTALI

Gli esami ematochimici risultavano nella norma, fatta eccezione per una lieve alterazione degli indici di funzionalità renale e anemia; la ricerca del sangue occulto nelle feci era anch'essa negativa.
Eseguiva una TC torace-addome a strati sottili (12/06/2005) che evidenziava la presenza di fegato cirrotico, splenomegalia, circoli collaterali perisplenici, perigastrici e mesenterici; varici esofagee; versamento ascitico sovra e sotto-mesocolico; alcune millimetriche formazioni tondeggianti, iperdense nel contesto del ventaglio mesenterico come da carcinosi peritoneale. Negativi i reperti mediastinici e toracici.
I marcatori tumorali risultavano in parte alterati: CEA 5.23 ng/mL (<5), Ca125 1217,4 U/mL, (<35), CgA >1220 ng/mL (9-98), Ca19.9, NSE, alfaFP e PSA nella norma.
Veniva pertanto inviato ad un reparto di chirurgia e sottoposto a laparoscopia diagnostica, con biopsia epatica e dei noduli peritoneali, drenaggio del liquido ascitico.
L'esame istologico dimostrava la presenza di cirrosi epatica; carcinosi peritoneale Cromogranina A +, Sinaptofisina +, NSE -, S100 -.
Nell'impossibilità di eseguire l'Octreoscan, il paziente eseguiva PET total-body con FDG (17/07/2005) (Figura 1) che rilevava la presenza di diffuso, relativo iperaccumulo del tracciante di pertinenza peritoneale, disposto a grembiule in corrispondenza della parete anteriore dell'addome.

LE CONCLUSIONI DIAGNOSTICHE

Veniva diagnosticata carcinosi peritoneale da neoplasia ad origine primitiva sconosciuta con componente neuroendocrina.

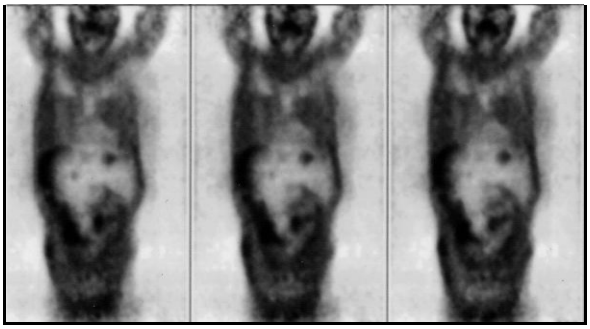

Figura 1. Tomoscintigrafia globale corporea del 11/7/2005

LA TERAPIA E IL DECORSO CLINICO

Nel mese di Luglio 2005 iniziava pertanto chemioterapia con Carboplatino AUC 4 g1, Paclitaxel 70 mg/m^2 g1,8 ogni 21 giorni per 3 cicli, e trattamento con Lanreotide 30 mg 1 fl i.m. ogni 28 giorni. Le tossicità riscontrate, un episodio di neutropenia febbrile e due di diarrea refrattaria, determinavano il prolungamento dell'intervallo interciclo. La rivalutazione della malattia mediante TC torace-addome (03/01/2006) e PET (03/02/2006) (Figura 2) mostravano parziale regressione della patologia peritoneale. Si osservavano inoltre normalizzazione del CEA 4.79 ng/mL (<5) e significativa riduzione della CgA 214 ng/mL (9-98).

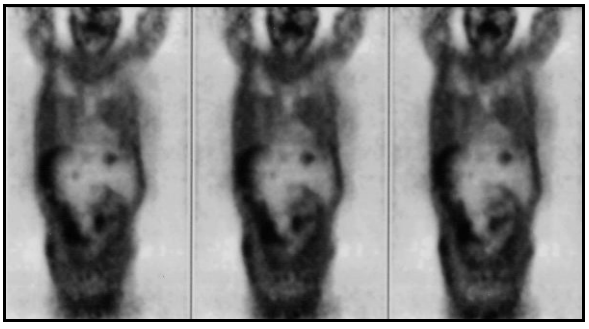

Figura 2. Tomoscintigrafia globale corporea del 3/2/2006

Nonostante la buona risposta ottenuta, considerate le tossicità riscontrate, si sospendeva la chemioterapia e proseguiva Lanreotide. Le successive rivalutazioni dimostravano una stabilizzazione della malattia fino a novembre 2006, quando sia la TC torace-addome (29/11/2006) che la PET (15/12/2006) (Figura 3) identificavano la presenza di progressione polmonare. A Gennaio 2007 il paziente riprendeva il trattamento chemioterapico secondo lo schema precedente (con riduzione del Paclitaxel a 60 mg/m^2) che sospendeva dopo 4 cicli (Maggio 2007) per trombocitopenia persistente G3-4. La rivalutazione confermava la presenza della malattia a livello peritoneale ma non evidenziava più la localizzazione polmonare. Si osservava inoltre normalizzazione della CgA. Ha proseguito fino ad oggi terapia con Lanreotide.

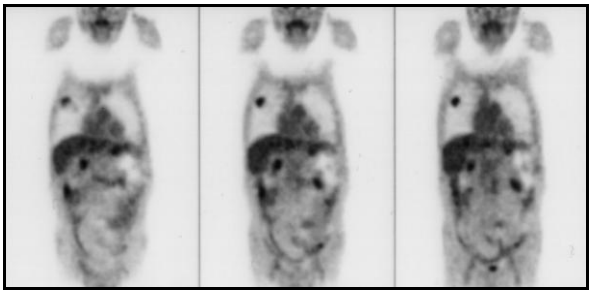

Figura 3. Tomoscintigrafia globale corporea del 15/12/2006

LA DISCUSSIONE

Le successive rivalutazioni di malattia, da Settembre 2007 ad oggi, hanno mostrato una risposta completa: negativizzazione reperti TC e PET (Figura 4) e normali livelli di CgA (ultimo dosaggio Aprile 2008 2.9 ng/mL, v.n. 0-100). Il paziente è in condizioni cliniche generali buone (ECOG-PS 0) prosegue i controlli previsti.

Il sito di origine di un carcinoma istologicamente determinato non viene identificato in circa il 3% dei pazienti [45]: questi tumori vengono generalmente chiamati a primitività ignota. Essi rappresentano un gruppo autonomo ed eterogeneo, che si presenta alla prima diagnosi con una o più lesioni secondarie, la cui origine non può essere individuata dopo anamnesi approfondita, esame obiettivo e opportune procedure di diagnostica [46]. Gli istotipi più frequenti sono l'adenocarcinoma e il carcinoma indifferenziato, seguono poi altri tipi istologici quali squamo-cellulari, tumori neuroendocrini, melanomi e sarcomi.

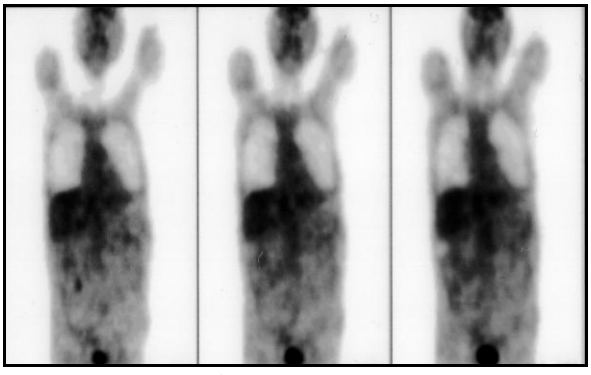

Figura 4. Tomoscintigrafia globale corporea del 13/09/2007

La sopravvivenza di questi pazienti supera raramente i 12 mesi e meno del 10% di loro è vivo a 5 anni [47]. La maggior parte di questi tumori è refrattaria ai trattamenti sistemici, cosicchè l'individuazione di gruppi a migliore prognosi, che possano beneficiare di specifici trattamenti è di fondamentale importanza. Attualmente non esiste uno standard di trattamento, anche se schemi a base di Cisplatino hanno portato buoni tassi di risposta [48]. Negli ultimi anni i nuovi farmaci sono stati ampiamente indagati ed hanno fornito risultati incoraggianti [49, 50]

Nel nostro caso, è stato scelto uno schema a base di platino, con il Carboplatino preferito al Cisplatino per via dell'alterata funzionalità renale del paziente, in associazione a Paclitaxel.

L'istotipo neuroendocrino, unitamente agli elevati livelli di CgA, hanno suggerito l'associazione di un analogo della somatostatina. Il risultato ottenuto, sia in termini di risposta, che di sopravvivenza ha superato

ogni aspettativa e può aggiungere nuove motivazioni per la ricerca di trattamenti il più possibile specifici ed individualizzati per questo tipo di pazienti.

BIBLIOGRAFIA

1.Pavlidis, N. and Fizazi, K. Cancer of unknown primary (CUP). Crit Rev Oncol Hematol, 54: 243-250, 2005.
2.Greco, F. A. and Hainsworth, J. D. Tumors of unknown origin. CA Cancer J Clin, 42: 96-115, 1992.
3.Culine, S., Kramar, A., Saghatchian, M., Bugat, R., Lesimple, T., Lortholary, A., Merrouche, Y., Laplanche, A., and Fizazi, K. Development and validation of a prognostic model to predict the length of survival in patients with carcinomas of an unknown primary site. J Clin Oncol, 20: 4679-4683, 2002.
4.Bugat, R., Bataillard, A., Lesimple, T., Voigt, J. J., Culine, S., Lortholary, A., Merrouche, Y., Ganem, G., Kaminsky, M. C., Negrier, S., Perol, M., Laforet, C., Bedossa, P., Bertrand, G., Coindre, J. M., and Fizazi, K. Summary of the Standards, Options and Recommendations for the management of patients with carcinoma of unknown primary site (2002). Br J Cancer, 89 Suppl 1: S59-66, 2003.
5. Briasoulis, E., Kalofonos, H., Bafaloukos, D., Samantas, E., Fountzilas, G., Xiros, N., Skarlos, D., Christodoulou, C., Kosmidis, P., and Pavlidis, N. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. J Clin Oncol, 18: 3101-3107, 2000.
6. Greco, F. A., Burris, H. A., 3rd, Litchy, S., Barton, J. H., Bradof, J. E., Richards, P., Scullin, D. C., Jr., Erland, J. B., Morrissey, L. H., and Hainsworth, J. D. Gemcitabine, carboplatin, and paclitaxel for patients with carcinoma of unknown primary site: a Minnie Pearl Cancer Research Network study. J Clin Oncol, 20: 1651-1656, 2002.

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REVIEW ARTICLE

Should cirrhosis change our attitude towards treating non-hepatic cancer?

Giuseppe Cabibbo[1,2,*], Laura Palmeri[3,*], Sergio Palmeri[3] and Antonio Craxi[1]

1 Sezione di Gastroenterologia, DiBiMIS, University of Palermo, Palermo, Italy
2 Dipartimento di Biopatologia e Metodologie Biomediche, University of Palermo, Palermo, Italy
3 Cattedra di Oncologia Medica, Dipartimento di Discipline Chirurgiche ed Oncologiche, University of Palermo, Palermo, Italy

Keywords
chemotherapy – cirrhosis – hepatotoxicity – non-hepatic cancer

Abbreviations
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NHC, non-hepatic cancers.

Correspondence
Dr Giuseppe Cabibbo, Sezione di Gastroenterologia,
Dipartimento Biomedico di Medicina Interna e Specialistica,
University of Palermo,
Piazza delle Cliniche 2,
90127 Palermo, Italy
Tel.: +39 091 655 2280
fax: +39 091 655 2156
e-mail: g.cab@libero.it

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Abstract

Cirrhosis is a major cause of morbidity and mortality and is the end stage of any chronic liver disease. Cancer, a leading cause of death worldwide, is a growing global health issue. There are limited data in the literature on the incidence, prevalence and management of non-hepatic cancers (NHC) in cirrhotic patients. The aim of this brief review was to underline the main concerns, pitfalls and warnings regarding practice for these patients.

Survival of patients with compensated cirrhosis is significantly longer than that of decompensated cirrhosis and patients with NHC and in Child-Pugh class C should not be candidates for cytotoxic chemotherapy. It is important before starting cytotoxic chemotherapy to assess the aetiology and stage of liver disease and to screen these patients for portal hypertension and fluid retention. During cytotoxic chemotherapy, the effectiveness of cancer treatment, as well the appearance of early signs of hepatic decompensation, must be thoroughly monitored. Future phase 3 trial designs in oncology should include a share of patients with compensated cirrhosis to obtain specific information in this setting. Identification of tests able to measure the global degree of hepatic impairment caused by cirrhosis could help in the management of this particular clinical situation.

Non-hepatic cancers (NHC) and cirrhosis are common conditions, each of them representing a leading cause of death worldwide. It has been estimated that there were 7.6 million cancer-related deaths worldwide in 2007 (1), while deaths attributable to chronic liver disease were 1.28 million in 1990 (2.5% of global deaths) (2). Hence, by the pure laws of mathematics, one could estimate that at least 190 000 patients with solid organ malignant tumours also have cirrhosis.

The issue of comorbidity may be more complicated, since in the senior age fascia, when cirrhosis is more prevalent, colon or gastric cancer is distinctly more frequent. Other factors, either constitutional (male gender) or acquired (obesity, alcohol abuse), may act as further confounders. Nonetheless, only hepatocellular carcinoma (HCC) is typically associated with cirrhosis as a problem in clinical practice. It is arduous to estimate the incidence of cancer other than HCC in patients with cirrhosis. Little data can be retrieved from the literature (3–7) and they show that incidence and management were, and probably still are, controversial. However, an interesting recently published article shows that the overall risk for non-HCC malignancies is more than two-fold greater for patients with cirrhosis (mostly biliary and gastrointestinal malignancies) than for the general population (8).

When facing patients with NHC who have cirrhosis, clinicians may encounter some difficulties both in terms of choosing the appropriate treatment for cancer and of managing treatment-related hepatotoxicity and adverse liver events. In this brief review, we aimed to underline the main concerns, pitfalls and warnings regarding practice for these patients.

Cirrhosis and survival of the patient with non-hepatic cancer

It is difficult to estimate the real prevalence of cirrhosis in the general population, as the disease is mostly asymp-

*Both authors contributed equally to this study.

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tomatic until the patient develops liver failure. The prognosis of cirrhosis is highly variable, being influenced by a number of factors, including disease stage, aetiology and feasibility of eradicating the aetiological factors and presence of complications and comorbidities. More than 30 years ago, Child and Turcotte designed a scoring system that, with a few modifications by Pugh, remains the most widely used for prognostic classification of cirrhotic patients (9). Survival of patients with compensated cirrhosis is significantly longer than that of decompensated patients, with median survival times of >12 years and 2 years respectively (10).

As the outcome in a patient with non-hepatic cancer (NHC) and decompensated (particularly Child-Pugh C) cirrhosis is related mostly to the hepatic functional impairment rather than to the neoplastic disease, it seems reasonable to say that these patients, in general, should not be candidates for cytotoxic treatments (Fig. 1). For Child-Pugh B patients, the effective degree of hepatic disfunction must be carefully evaluated, together with the tumour/patient characteristics (e.g. chemo-sensitivity, site of disease, kind and degree of symptoms), as suggested by the experience with hepatocellular carcinoma (HCC) patients treated with sorafenib (11). It must be stressed that no formal experience or dosing recommendations are available in this setting, even for the most common cytotoxic agents, and that problems related to altered hepatic drug metabolism may be overwhelming.

Conversely, the oncological management of a patient with compensated (Child A) cirrhosis developing NHC is a matter of interest and poses various unresolved clinical questions. Few quality data are available, for a number of reasons:

(i) Most clinical trials in oncology exclude patients with any degree of impaired hepatic function or with cirrhosis. To date, neither the regulatory agencies nor the worldwide industry has ever prompted the inclusion of such patients in trials of oncological agents. This dramatically reduces the possibility of managing this comorbidity with an evidence-based approach.
(ii) Many cytotoxic drugs are metabolized by the liver, where some drugs are inactivated to non-toxic, excretable metabolites or else activated if they are pro-drugs. Hence, there are potential hazards in the administration of anti-cancer therapy to patients with an abnormal liver.

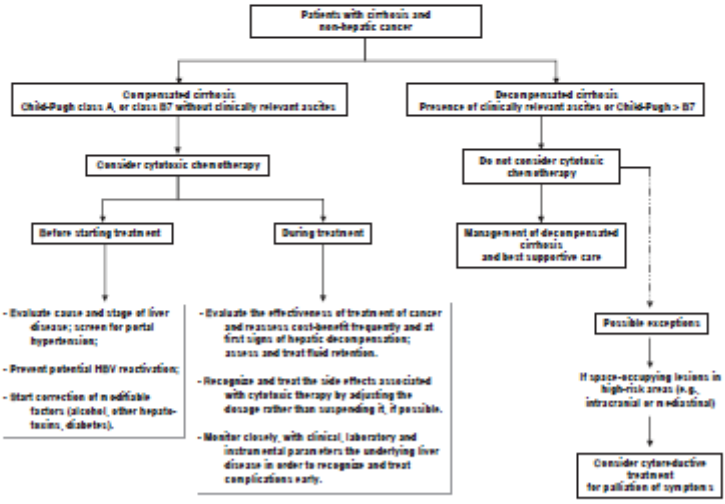

Fig. 1. Proposed decisional algorithm for patients with cirrhosis and non-hepatic cancer.

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(iii) As no single test reliably measures the global degree of hepatic impairment, biochemical estimation of liver function in patients with cancer may under- or overestimate the risk of hepatic toxicity.
(iv) Patients with cancer may carry a huge variety of metabolic paraneoplastic alterations (for instance, a condition of hypercoagulability) that could be of increased relevance in a cirrhotic patient and must be taken into account when approaching such patients. Moreover, many recent studies have indicated a prothrombotic state in patients with cirrhosis that can frequently induce portal vein thrombosis (PVT) during the course of the disease (12). Furthermore, cytotoxic chemotherapy and malignancies per se can determine a thrombophylic diathesis, which may facilitate, in turn, the occurrence of PVT in patients with slow portal flow because of portal hypertension.

Reactivation of hepatitis viruses [especially hepatitis B virus (HBV)], the main cause of cirrhosis worldwide, can be induced by chemotherapy and cause severe liver dysfunction in patients with cirrhosis. So, the existence of markers of the HBV infection must be systematically verified before starting chemotherapy. This problem is carefully reviewed elsewhere (13–15).

Some major concerns arise for the clinician facing an oncological patient with compensated cirrhosis.

Should that patient be treated?

As said, this depends mainly on the prognosis of the liver disease. The answer to this fundamental question must be affirmative when the patient's life expectancy is not, or only marginally, influenced by the liver disease. In other words, it is our opinion that NHC should always be treated when it affects the ultimate prognosis of a patient with compensated cirrhosis and a life expectancy of more than 3 months. The choice of treatment must, however, take into account the effect that the oncological drugs by themselves may have on liver disease and mostly how hepatic decompensation ensuing from them will affect the possibility of the completion of the intended protocol. Clearly, other conditions potentially affecting pharmacokinetics and pharmacodynamics of the antineoplastic agents, increasing toxicities and/or reducing effectiveness, should be carefully taken into account. For example, elderly patients can have a decrease in volume of distribution, glomerular filtration rate, hepatic metabolism, intestinal absorption or levels of enzymes like dihydropyrimidin dehydrogenase, but also an increase in the expression of multidrug resistance gene, as well as decreased apoptosis, and decreased cell proliferation rate (16).

Which drugs are most appropriate?

After a thorough assessment of the liver status, otherwise healthy, compensated cirrhotic patients with NHC should be treated according to the standard of care for their specific neoplastic disease. The pharmacokinetic and pharmacodynamic characteristics of the drugs, together with the tolerability profile, must be kept in mind. Two interesting reviews on the topic of liver function in oncology have been recently published (17, 18).

Here, we briefly examine the profiles of some of the most widely used anticancer drugs. The entire class of fluoropyrimidines can reasonably be taken into consideration as therapy because even if their primary metabolism is hepatic they are eliminated mainly through the kidney (19, 20). Moreover, it has recently been shown that, in animal models, hepatic fibrosis does not affect the pharmacokinetics of 5-fluorouracil (5-FU) (21). Antineoplastic antibiotics, such as doxorubicin, can be used as they rarely cause direct hepatic injury, which usually consists in transient aminotransferases and bilirubin increases on an idiosyncratic basis, while their cardiotoxic effects should be closely monitored (22). Microtubule disrupting agents (e.g. taxanes, vinorelbine) should be used cautiously as they cause (generally reversible) direct hepatic injuries in about one-third of patients on high doses. However, two questions must be considered: (i) patients with elevated bilirubin, or abnormal aminotransferases and alkaline phosphatase levels are at increased risk for the development of grade 4 side effects; and (ii) severe fluid retention can occur in about 6% of patients despite use of an adequate dexamethasone premedication, which could be of major relevance in cirrhotic patients who avidly retain sodium and fluids (23).

With regard to combination regimens, very few specific data are available. Some information on their toxicity profile in cirrhotic patients can be obtained from published papers concerning chemotherapy combination regimens used in advanced HCC superimposed on cirrhosis. For example, gemcitabine-oxaliplatin combined with cetuximab, capecitabine-oxaliplatin with bevacizumab, 5-FU-oxaliplatin and leucovorin, 5-FU-cisplatin-mitoxantrone and capecitabine-oxaliplatin was recently evaluated for advanced HCC (24–28). Major toxicities (grade 3 or 4) included myelosuppression (neutropenia and thrombocitopenia), skin toxicity, neurotoxicity, fatigue, hand-foot syndrome, diarrhoea, renal toxicity, bleeding and infection. Only with the combination of capecitabine and oxaliplatin was elevation of transaminases and/or bilirubin reported. Overall, toxicities observed with these regimens are manageable in cirrhotic patients and liver toxicities are unusual.

Not much is known about molecular-targeted therapies in cirrhotic patients. Most data come from studies on the treatment of HCC with the multitargeted tyrosine kinase (TK) inhibitors sorafenib and sunitinib (29, 30). Though HCC is associated with cirrhosis, at least in the Western world, in more than 90% of patients (31, 32) in phase 3 studies (33, 34) used to register sorafenib for this indication, no specific attention was paid to the role of cirrhosis as a possible modifier of response and

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toxicity. An unspecified proportion of patients enrolled in these studies had cirrhosis, but most were reported as Child A. A *post hoc* analysis showed comparable toxicity and efficacy in the few Child B patients (35). Moreover, in the phase 2 trial in which 99 Child-Pugh A and 38 Child-Pugh B patients were enrolled, the pharmacokinetics of sorafenib was not influenced by the Child-Pugh class (36).

Treatment with sunitinib was instead found to be associated with a high proportion of patient (about 10%) death from treatment-related causes. Gastrointestinal haemorrhage was also reported.

As concerns anti-epidermal growth factor receptor TK inhibitors, few data are available from a phase 1 study that evaluated the drug's pharmacokinetics in patients with liver dysfunction (defined as aspartate aminotransferase ≥ 3 times above normal, with or without albumin <25 g/L, or bilirubin 17–120 μmol/L, not necessarily related to cirrhosis)(37). Longer half-life, reduced clearance and increased proportion of dose-limiting toxic effects were observed. The lack of data in this specific field makes it difficult to reach definitive conclusions and competitive research will likely continue over the coming years.

Finally, interesting data have been published concerning the use of bevacizumab in non-cirrhotic patients with liver metastases. In fact, decreased severity of the sinusoidal obstruction syndrome and no impact on hepatic steatosis and fibrosis have been reported, suggesting a positive effect of the drug on the liver tissue (38, 39).

An unanswered question concerning the use of antiangiogenics in cirrhotic patients is, in fact, their effect on portal hypertension, though recent experimental work with sorafenib seems to suggest a possible role of this drug in reducing portal hypertension, according to data from animal models (40).

Despite the absence of solid evidence in this particular clinical setting, we believe that antineoplastic agents can be used, though with caution, in patients with compensated cirrhosis and NHC. Today, little specific data are available on the use of molecular-targeted therapies.

Are normally expected adverse events of the chosen regimen worse in cirrhotic patients, and if so, how to manage and/or prevent them?

This is conceivably the principal concern when treating a cirrhotic patient with NHC. The main expected toxic effects of the most widely used anti-neoplastic drugs should be considered when choosing treatment and promptly managed when they manifest. Many drugs particularly 5-FU, oxaliplatin and irinotecan have an intrinsic liver toxicity (mainly increased aminotransferases and bilirubin) that may exacerbate the underlying liver disease and, in principle, should be avoided or administered cautiously. Clearly this is only feasible when there are possible alternative regimens.

Many usually expected, easily manageable adverse events may have increased relevance in cirrhotic patients. For instance, leucopenia and thrombocytopenia, which are resulting from splenic sequestration secondary to portal hypertension, can magnify the effects of bone marrow suppression caused by antineoplastic agents. Similarly, it must be kept in mind that the equilibrium of the clot cascade is always at risk of alteration in these patients, as a consequence of paraneoplastic syndromes, chemotherapeutic agents and cirrhosis itself, among other factors. All of these can induce PVT, which in turn may worsen the prognosis of patients with compensated cirrhosis. So, because early diagnosis of acute PVT and anticoagulation are probably the main determinants of improved survival (41), in our opinion, such patients should have frequent (every 2–3 months) ultrasound evaluation and pulsed-Doppler assessment of the portal flow to start an appropriate anticoagulation treatment as early as possible, though this is not current practice.

How, and how often, should the patient's liver status be assessed?

As no specific guidelines exist, close co-operation between the oncologist and the hepatologist is recommended, together with a cautious approach during the decision-making process, to give the best care to cancer patients with cirrhosis.

Liver function itself (an imperfect concept, encompassing hundreds of different activities performed by hepatic parenchymal and non-parenchymal cells) may not be stable over time. In clinical practice, it would be preferable to evaluate liver status as a whole through a complex evaluation that encompasses clinical evaluation and biochemical and instrumental parameters. The Child-Pugh score and the Model for End-Stage Liver Disease (MELD) are useful tools and adopted daily by hepatologists (42). These should be added to the common pretreatment laboratory examinations and recalculated before each chemotherapy cycle. However, these traditional scoring systems have several shortcomings. The variables in the Child-Pugh score are limited by a lack of consistency and reproducibility; for example, ascites and hepatic encephalopathy are graded subjectively and may be altered substantially by medical interventions (e.g. the use of diuretics for ascites or lactulose and rifaximin for encephalopathy). Bilirubin levels may depend on the aetiology of liver disease (e.g. primary biliary cirrhosis or primary sclerosing cholangitis), while low albumin plasma levels could also be related to the nutritional status and to a catabolic state secondary to malignancy.

On the other hand, the MELD score has been validated almost exclusively in advanced liver disease and for short-term prognosis. It must be remembered that aminotransferases, though a sensitive index of hepatocellular necrosis, can be misleading as an indicator of

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Table 1. The NCI-ODWG (43) criteria for stratifying patients according to liver dysfunction into five groups, from normal liver function (A) to need for liver transplant (E)

Group Liver function	Group A Normal	Group B Mild	Group C Moderate	Group D Severe	Group E Liver transplant
Total bilirubin AST	≤ ULN ≤ ULN	B1: ≤ ULN B2: >1.0–1.5 × ULN B1: >ULN B2: Any value	>1.5–3 × ULN Any value	>3 × ULN Any value	Any value Any value

A, normal; B, mild dysfunction; C, moderate dysfunction; D, severe dysfunction; E, liver transplant.
AST, aspartate aminotransferase; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; ULN, upper limit of normal range.

hepatotoxicity, as they are bound to fluctuate, sometimes widely, also in relation to the aetiology of the underlying liver disease, especially in viral (HBV and HCV) cirrhosis. With specific reference to the liver function and/or dysfunction evaluation in the field of oncology, the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) suggested different criteria that utilize two objective, readily measurable, laboratory parameters, specifically total bilirubin (TB) and aspartate aminotransferase (AST).

National Cancer Institute Organ Dysfunction Working Group criteria classify liver dysfunction into four classes: normal [TB and AST < upper limit of normal (ULN)] and mild (TB > ULN to 1.5 × ULN or AST > ULN) function, in which dose modification of chemotherapeutic agents is usually not necessary, or moderate (TB > 1.5–3 × ULN, any AST) and severe [TB > 3–10 × ULN, any AST(43)] in which dose modification may be necessary (Table 1). Interestingly, a prospective comparison between the NCI and the Child-Pugh score has been carried out in a phase 1 study (44). Unfortunately, no definitive results emerged and urgent calls for a more comprehensive, as well as specific, evaluation tool are expected in the literature. Moreover, the use of the NCI-ODWG criteria has never been validated for the assessment of liver function in cancer patients with cirrhosis.

In our opinion, because there is still no specific indication for the management of cirrhotic patients treated with chemotherapy for NHC, a routine multidisciplinary approach, involving hepatologists and oncologists, is required to provide optimal care to these patients.

In other words, while waiting for a formal and validated scale to be used routinely for this setting of patients, oncologists are urged to add a consultation by a hepatologist to the usual prechemotherapy patient assessment (performance status, clinical examinations, biochemistry). Conversely, hepatologists are urged to consult an oncologist before deciding that a Child-Pugh A/B patient carrying an NHC is not a good candidate for an antitumoural treatment.

Conclusions and recommendations

To date, the appropriate strategy for effective and safe chemotherapy treatment of cancer patients with compensated cirrhosis has not been defined. It is well known that there is heterogeneity among cancer patients in terms of pharmacokinetics and pharmacodynamics. Generally, the overall effect of liver disease on drug pharmacokinetics is determined by the alterations produced in the processes of absorption, distribution and elimination. For these reasons, the oncologist prescribing anti-neoplastic therapy must carefully consider characteristics, route of administration, dose and dosing interval.

Since, as already mentioned, most clinical trials exclude patients with impaired hepatic function, available knowledge about individual chemotherapeutic agents in the setting of cirrhosis is based on small, retrospective studies or on trials investigating drugs for hepatocellular carcinoma (HCC) superimposed on compensated cirrhosis. Very few agents have, in fact, undergone formal phase 1 studies to test their pharmacokinetics and tolerability in patients with liver dysfunction, while empirical guidelines are frequently used in clinical practice because the phase 1 findings have not been further tested in phase 2 and 3 settings (45–50). As previously noted, the lack of compensated cirrhotic patients in large phase 3 studies may lead to two different conditions: firstly, physicians might deny antitumour treatment to cirrhotic patients because of lack of evidence-based data; secondly, physicians empirically consider treating these patients without evidence and/or the possibility of comparing efficacy and safety of therapy. Consequently, the physician who plans treatment of a non-hepatic cancer in a patient with compensated cirrhosis is burdened, in the absence of any guideline for this specific type of patient, by the narrow therapeutic index, if any, of cytotoxic drugs, on one hand, and the complicated safety issues typical of such patients, on the other. The way to solve this clinical dilemma is to overcome, in principle, the prejudice that a cirrhotic patient cannot be treated if he/she develops a cancer other than HCC. Clinical researchers, health authorities and regulatory agencies must start including, or require inclusion of, a share of patients with compensated cirrhosis in large randomized controlled trials when investigating medical treatment of any cancer. Moreover, future clinical trial designs should include stratification of patients according to their basal liver function. An open question remains whether patients with tumour-related organ dysfunction should be approached differently than those with baseline (non-tumour-related) organ dysfunction.

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A few final recommendations can be made (Fig. 1):

(i) Before starting treatment with cytotoxic chemotherapy, physicians should:

(a) carefully evaluate aetiology (virus, alcohol, others) and stage of liver disease (liver status with Child-Pugh and Model for End-Stage Liver Disease scores), screen for portal hypertension, evaluate fluid retention;
(b) prevent possible viral reactivation with lamivudine, when necessary (hepatitis B virus) and
(c) start correction of modifiable causal factors (alcohol, other hepato-toxins, diabetes).

(ii) During cytotoxic chemotherapy, physicians should:

(a) evaluate the effectiveness of treatment of cancer and reassess cost-benefit frequently and at first signs of hepatic decompensation;
(b) recognize and treat the side effects associated with cytotoxic therapy by adjusting the dosage rather than suspending if possible and
(c) closely monitor, using clinical, laboratory and instrumental parameters, the underlying liver disease to recognize and treat early complications.

(iii) As concerns liver disease, treatment and follow-up parameters should not change in terms of overall strategy except to accommodate the more frequent controls needed for cancer therapy. Treatment that may cause cytopenia, such as IFN-based antiviral therapies, must clearly be avoided or postponed in this setting.

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References

1. Thun MJ, Delancey JO, Center MM, Jemal A, Ward EM. The global burden of cancer: priorities for prevention. *Carcinogenesis* 2010; 31: 100–10.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; 349: 1269–76.
3. Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V, Collier J. Liver cirrhosis, other liver diseases, pancreatitis and subsequent cancer: record linkage study. *Eur J Gastroenterol Hepatol* 2008; 20: 384–92.
4. Melato M, Laurino L, Macli F, Valente M, Okuda K. Relationship between cirrhosis, liver cancer, and hepatic metastases. An autopsy study. *Cancer* 1989; 64: 455–9.
5. Seymour K, Charnley RM. Evidence that metastasis is less common in cirrhotic than normal liver: a systematic review of post-mortem case-control studies. *Br J Surg* 1999; 86: 1237–42.
6. Sorensen HT, Friis S, Olsen JH, *et al*. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* 1998; 28: 921–5.
7. Zatti S, Piccigallo E, Rampinelli L, *et al*. Primary and metastatic tumors of the liver associated with cirrhosis. A study based on laparoscopy and autopsy. *Gastrointest Endosc* 1986; 32: 91–5.
8. Kalaitzakis E, Gunnarsdottir SA, Josefsson A, Bjornsson E. Increased risk for malignant neoplasms among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; 9: 168–74.
9. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60: 646–9.
10. D'amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006; 44: 217–31.
11. Zhu AX, Clark JW. Commentary: Sorafenib use in patients with advanced hepatocellular carcinoma and underlying Child-Pugh B cirrhosis: evidence and controversy. *Oncologist* 2009; 14: 67–9.
12. Lisman T, Caldwell SH, Burroughs AK, *et al*. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol* 2010; 53: 362–71.
13. Kohrt HE, Ouyang DL, Keeffe EB. Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 2006; 24: 1003–16.
14. Hoofnagle JH. Reactivation of hepatitis B. *Hepatology* 2009; 5(5 Suppl): S156–65.
15. Marzano A, Angelucci E, Andreone P, *et al*. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 2007; 39: 397–408.
16. Haddad A, Shepard D. Geriatric oncology and palliative medicine. *Semin Oncol* 2011; 38: 362–6.
17. Field KM, Dow C, Michael M. Part I: Liver function in oncology: biochemistry and beyond. *Lancet Oncol* 2008; 9: 1092–101.
18. Field KM, Michael M. Part II: Liver function in oncology: towards safer chemotherapy use. *Lancet Oncol* 2008; 9: 1181–90.
19. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA. Hepatic toxicity associated with fluorouracil plus levamisole adjuvant therapy. *J Clin Oncol* 1993; 11: 2586–90.
20. Peppercorn PD, Reznek RH, Wilson P, Slevin ML, Gupta RK. Demonstration of hepatic steatosis by computerized tomography in patients receiving 5-fluorouracil-based therapy for advanced colorectal cancer. *Br J Cancer* 1988; 77: 2008–11.
21. Nagata M, Hidaka Y, Hatakeyama K, *et al*. Hepatic fibrosis does not affect the pharmacokinetics of 5-fluorouracil in rats. *Biopharm Drug Dispos* 2011; 32: 126–30.
22. Avilés A, Herrera J, Ramos F, *et al*. Hepatic injury during doxorubicin therapy. *Arch Pathol Lab Med* 1984; 108: 912–3.
23. Huizing MT, Misser VH, Pieters RC, *et al*. Taxanes: a new class of antitumor agents. *Cancer Invest* 1995; 13: 381–404.
24. Asnacios A, Fartoux L, Romano O, *et al*. Gemcitabine plus oxaliplatin (GEMOX) combined with cetuximab in patients with progressive advanced stage hepatocellular

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carcinoma: results of a multicenter phase 2 study. *Cancer* 2008; 112: 2733–9.
25. Boige V, Raoul JL, Pignon JP, *et al.* Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. *Br J Cancer* 2007; 97: 862–7.
26. Corsini R, Mir O, Casset A, *et al.* Feasibility of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) in cirrhotic or liver transplant patients: experience in a cohort of advanced hepatocellular carcinoma patients. *Invest New Drugs* 2010. DOI: 10.1007/s10637-010-9525-0 [Epub ahead of print].
27. Sun W, Sohal D, Haller DG, *et al.* Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. *Cancer* 2011; 117: 3187–92.
28. Yeh CT, Chen HC, Sung CM, *et al.* Retrospective comparison between a regular and a split-dose protocol of 5-fluorouracil, cisplatin, and mitoxantrone for the treatment of far advanced hepatocellular carcinoma. *BMC Cancer* 2011; 11: 117.
29. Di Maio M, Daniele B, Perrone F. Targeted therapies: role of sorafenib in HCC patients with compromised liver function. *Nat Rev Clin Oncol* 2009; 6: 505–6.
30. Faivre S, Raymond E, Boucher E, *et al.* Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol* 2009; 10: 794–800.
31. El-Serag HB, Davila JA, Petersen NJ, Mcglynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003; 139: 817–23.
32. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; 362: 1907–17.
33. Cheng AL, Kang YK, Chen Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25–34.
34. Llovet JM, Ricci S, Mazzaferro V, *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378–90.
35. Bruix J, Raoul JL, Sherman M, *et al.* Efficacy and safety of sorafenib in patients with hepatocellular carcinoma (HCC): subanalysis of SHARP trial based on Barcelona Clinic Liver Cancer (BCLC) stage. *J Hepatol* 2009; 50(Suppl): S28.
36. Abou-Alfa GK, Schwartz L, Ricci S, *et al.* Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; 24: 4293–300.
37. Miller AA, Murry DJ, Owzar K, *et al.* Phase I and pharmacokinetic study of erlotinib for solid tumors in patients with hepatic or renal dysfunction: CALGB 60101. *J Clin Oncol* 2007; 25: 3055–60.
38. Klinger M, Eipeldauer S, Hacker S, *et al.* Bevacizumab protects against sinusoidal obstruction syndrome and does not increase response rate in neoadjuvant XELOX/FOLFOX therapy of colorectal cancer liver metastases. *Eur J Surg Oncol* 2009; 35: 515–20.
39. Rubbia-Brandt L, Lauwers GY, Wang H, *et al.* Sinusoidal obstruction syndrome and nodular regenerative hyperplasia are frequent oxaliplatin-associated liver lesions and partially prevented by bevacizumab in patients with hepatic colorectal metastasis. *Histopathology* 2010; 56: 430–9.
40. Mejias M, Garcia-Pras E, Tiani C, *et al.* Beneficial effects of sorafenib on splanchnic, intrahepatic, and portocollateral circulations in portal hypertensive and cirrhotic rats. *Hepatology* 2009; 49: 1245–56.
41. Primignani M. Portal vein thrombosis, revisited. *Dig Liver Dis* 2010; 42: 163–70.
42. Kamath PS, Wiesner RH, Malinchoc M, *et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33: 464–70.
43. Available at http://ctep.cancer.gov/protocoldevelopment/docs/hepatic_dysfunction_y3.doc. Accessed 20 November 2010.
44. Patel H, Egorin MJ, Remick SC, *et al.* Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): Implications for chemotherapy dosing. *J Clin Oncol* 2004; ASCO Annual Meeting Proceedings (Post-Meeting Edition). 22 (14S): abstract 6051.
45. Fleming GF, Schilsky RL, Schumm LP, *et al.* Phase I and pharmacokinetic study of 24-hour infusion 5-fluorouracil and leucovorin in patients with organ dysfunction. *Ann Oncol* 2003; 14: 1142–7.
46. O'reilly S, Rowinsky E, Slichenmyer W, *et al.* Phase I and pharmacologic studies of topotecan in patients with impaired hepatic function. *J Natl Cancer Inst* 1996; 88: 817–24.
47. Raymond E, Boige V, Faivre S, *et al.* Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. *J Clin Oncol* 2002; 20: 4303–12.
48. Vernook AP, Egorin MJ, Rosner GL, *et al.* Phase I and pharmacokinetic trial of paclitaxel in patients with hepatic dysfunction: Cancer and Leukemia Group B 9264. *J Clin Oncol* 1998; 16: 1811–9.
49. Vernook AP, Egorin MJ, Rosner GL, *et al.* Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. *J Clin Oncol* 2000; 18: 2780–7.
50. Vernook AP, Enders Klein C, Fleming G, *et al.* A phase I and pharmacokinetic study of irinotecan in patients with hepatic or renal dysfunction or with prior pelvic radiation: CALGB 9863. *Ann Oncol* 2008; 14: 1783–90.