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

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Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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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
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ABSTRACT

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.
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**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 glycaminamide ribonucleotide 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
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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.
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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:
  o Neutrophil count ≥1.5x10^9/L
  o Platelet count ≥100x10^9/L
  o Leucocyte count > 3,000/mm
  o Hemoglobin ≥ 9 g/dL
• Hepatic Function:
  o Total bilirubin ≤ 1.5 time the upper normal limit (UNL)
  o ASAT ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
  o ALAT ≤ 2.5xUNL in absence of liver metastases, or ≤5xUNL in presence of liver metastases
• Renal Function: serum creatinine ≤1.5xUNL
• Metabolic Function
  o Magnesium ≥ lower limit of normal.
  o 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
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- 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.
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- Other exams will be performed as needed.

### 4.4 STUDY DESIGN

The treatment schedule includes:
- 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 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 length of observation will be at least of two cycles.

![Figure 1. Study flow chart](image)

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**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
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- 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>4</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60 y</td>
</tr>
<tr>
<td>Range</td>
<td>53-66</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Tumor Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>EGFR FISH +</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>N° of metastatic sites</strong></td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
<td>3</td>
</tr>
<tr>
<td>&gt;2</td>
<td>1</td>
</tr>
</tbody>
</table>
| 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).
**RESULTS**

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Sex</th>
<th>Male</th>
<th>Age</th>
<th>66</th>
<th>PS</th>
<th>1</th>
<th>Dose level</th>
<th>5.5 mg/kg</th>
<th>Nº of cy</th>
<th>2</th>
<th>Best response</th>
<th>SD</th>
<th>DLT</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2</td>
<td>Sex</td>
<td>Male</td>
<td>Age</td>
<td>63</td>
<td>PS</td>
<td>0</td>
<td>Dose level</td>
<td>5.5 mg/kg</td>
<td>Nº of cy</td>
<td>6 cy + 4 M</td>
<td>Best response</td>
<td>PR</td>
<td>DLT</td>
<td>No</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Sex</td>
<td>Male</td>
<td>Age</td>
<td>57</td>
<td>PS</td>
<td>0</td>
<td>Dose level</td>
<td>5.5 mg/kg</td>
<td>Nº of cy</td>
<td>6 cy</td>
<td>Best response</td>
<td>SD</td>
<td>DLT</td>
<td>no</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Sex</td>
<td>Female</td>
<td>Age</td>
<td>53</td>
<td>PS</td>
<td>0</td>
<td>Dose level</td>
<td>7.2 mg/kg</td>
<td>Nº of cy</td>
<td>1 cy</td>
<td>Best response</td>
<td>NE</td>
<td>DLT</td>
<td>No</td>
</tr>
</tbody>
</table>

PS, performance status; Nº, 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
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DISCUSSION

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+). Moreover, 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 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 molecular 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

Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

REFERENCES


Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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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.

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Principal subjects/occupational skills covered  
During her fellowship her interests are being focused on molecular aspects and clinical management of advanced lung cancer patients. Moreover she has been involved in a number of clinical trials sponsored by the pharmaceutical industries, the Italian Medicines Agency (AIFA) as well as by Independent Research Programs.

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Date  
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Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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 pharmaceutical industries, the Italian Medicines Agency (AIFA) as well as by Independent Research Programs.

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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)
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)
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.
ABSTRACT

Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

LAST THREE YEARS BOOK CHAPTER

"Neoplasie a sede primitiva sconosciuta"

LAST THREE YEARS FULL PAPERS


2.  “Role of loco-regional treatments for patients with breast cancer liver metastases”

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

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

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

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)”

2.  “Serum HER-2/neu (s-HER2) levels evaluation in breast cancer(BC) patients (PTS)”

3.  “Final results of a phase II trial of a weekly (W) poly-chemotherapy (CT) with cisplatin (CDDP), epirubicin (EPI), fluorouracil (5FU), folicin acid (FA) and G-CSF for the treatment of locally advanced (LA) or metastatic (M) gastroesophageal (GE) and gastric (G) cancer (C) patients (pts)”
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.


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”

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”.

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.
Weekly docetaxel in the treatment of metastatic breast cancer

Laura Palmieri
Marina Vaglica
Sergio Palmieri
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/m²) has been widely tested in several phase I and II studies both as a single agent and in multiple chemotherapy 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 hormone 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).
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

APPENDIX

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Objective response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>40-50</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>50-60</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>20-42</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>47-63</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>18-31</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>25-46</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>20-30</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>20-33</td>
</tr>
</tbody>
</table>


The taxanes

Thetaxanes, 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 began in the 1990s, with the first phase II trials demonstrating their antitumor activity as single agents (Holmes et al. 1991; Ringel et al. 1991; D’Andrea et al. 1997; Valero et al. 1999).

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 antracycline, 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. 1999; Seidman et al. 1999; Nahof et al. 1996, 1997).

In 2005, Gheris 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 (Gheris et al. 2003). 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 a significant difference between the two arms for OS (HR: 0.97; 95% CI = 0.87-1.07), although when the taxane used was docetaxel there was a significant difference in OS favoring taxane-containing regimens (HR: 0.88; 95% CI = 0.78-0.98). 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).
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

APPENDIX

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**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>
<thead>
<tr>
<th>Author and year of publication</th>
<th>N. of pts (BC pts)</th>
<th>Regimen</th>
<th>MTD - DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly single-agent docetaxel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomai et al 1994</td>
<td>21 (a)</td>
<td>Doc 50-65 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>55 mg/m² = neutropenia</td>
</tr>
<tr>
<td>Hainaut et al 1996</td>
<td>27 (7)</td>
<td>Doc 50-65 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>40 mg/m² = fatigue, anemia</td>
</tr>
<tr>
<td>Luce et al 1997</td>
<td>18 (a)</td>
<td>Doc 20-50 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>MTD not reached – no DLT</td>
</tr>
<tr>
<td>Loffler et al 1996</td>
<td>21 (a)</td>
<td>Doc 20-45 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>40-45 mg/m² = leukocytosis</td>
</tr>
<tr>
<td>Britz et al 1999</td>
<td>24 (1)</td>
<td>Doc 25-50 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>30 mg/m² = leukocytosis</td>
</tr>
<tr>
<td>Kourkoutis et al 2000</td>
<td>28 (19)</td>
<td>Doc 20-40 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>40 mg/m² = neutropenia</td>
</tr>
<tr>
<td>Nitschke et al 2003</td>
<td>26 (8)</td>
<td>Doc 20-40 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>35 mg/m² = anemia</td>
</tr>
<tr>
<td>Weekly docetaxel in combination with chemotherapeutic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast et al 2000</td>
<td>24 (a)</td>
<td>Doc 20-45 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>50 mg/m² = neutropenia</td>
</tr>
<tr>
<td>Tomai et al 2001</td>
<td>23 (1)</td>
<td>Doc 10-20 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>50 mg/m² = neutropenia</td>
</tr>
<tr>
<td>Wesel et al 2000</td>
<td>13 (a)</td>
<td>Doc 20-40 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>40 mg/m² = neutropenia</td>
</tr>
<tr>
<td>Sw VGA et al 2000</td>
<td>12 (a)</td>
<td>Doc 20-40 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>40 mg/m² = anemia, stomatitis, leukocytosis</td>
</tr>
<tr>
<td>Ishimaru et al 2007</td>
<td>11 (a)</td>
<td>Doc 20-45 mg/m² × 1 q 3 w × 6 (D) + 22</td>
<td>50 mg/m² = nausea, vomiting</td>
</tr>
</tbody>
</table>

*Abbreviations: BC, patients; BC, breast cancer; MTD, Maximum Tolerated Dose; DLT, dose limiting toxicity; w, week; Doc, docetaxel; Gen, gemcitabine; V/F, vinorelbine; Etopos, etoposide; Doc, doxorubicin; Cyc, cyclophosphamide.*
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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), 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 9.8%). Overall 24 patients (42.9%) were pre-treated with anthracyclines for MBC. The reported ORR was 33.4% including 4/60 CR (6.7%) and 16/60 PR (26.7%). Regarding toxicity, 23/62 (3.5%) cycles were associated with G3 neutropenia, and 2/62 (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.

Stemmerl 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 61 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 (Ahura et al 2002).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Recent selected phase II trials on weekly docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author and year of publication</strong></td>
<td><strong>N. of pts (line)</strong></td>
</tr>
<tr>
<td>Burstein et al 2000</td>
<td>29 (21% 2nd line)</td>
</tr>
<tr>
<td>Jackisch et al 2000</td>
<td>40 (90.2% 2nd or &gt; line)</td>
</tr>
<tr>
<td>Stemmerl et al 2001</td>
<td>25 (20% 2nd or &gt; line)</td>
</tr>
<tr>
<td>Alahur et al 2003</td>
<td>27 (21% 2nd or &gt; line)</td>
</tr>
<tr>
<td>Hainsworth et al 2004</td>
<td>41 (95.2% 2nd or &gt; line)</td>
</tr>
<tr>
<td>Ramos et al 2003</td>
<td>25 (all Anthra resistant)</td>
</tr>
<tr>
<td>D’Hondt et al 2003</td>
<td>36 (79% 2nd or &gt; line)</td>
</tr>
<tr>
<td>Stemmerl et al 2003</td>
<td>24 (1st line)</td>
</tr>
<tr>
<td>Ford et al 2004</td>
<td>42 (46.2% 2nd line)</td>
</tr>
</tbody>
</table>

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

Therapeutic and Clinical Risk Management 2004:33
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>N of pts (line)</th>
<th>Regimen</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornak et al 2001</td>
<td>37 (1st line)</td>
<td>VNR 20 mg/m² d1, d8 4w with Doc 20 mg/m² d1, d8 4w</td>
<td>64% at 1st line 32% at 2nd line</td>
</tr>
<tr>
<td>Palmieri et al 2005</td>
<td>38 (1st line)</td>
<td>Doc 25 mg/m² d1, d8 2w with Gem 400 mg/m² d1, d8 4w</td>
<td>64% (50 evaluable)</td>
</tr>
<tr>
<td>Pizzo et al 2004</td>
<td>29</td>
<td>Doc 20 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>44%</td>
</tr>
<tr>
<td>Etsera et al 2002</td>
<td>20 (19, 2nd line)</td>
<td>Doc 25 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>68%</td>
</tr>
<tr>
<td>Rando et al 2002</td>
<td>12 (1st line)</td>
<td>Doc 20 mg/m² q2w with T 1 mg/m² q2w + Doc 100 mg/m² d1 q2w</td>
<td>Overall 42%</td>
</tr>
<tr>
<td>Telesco et al 2004</td>
<td>14 (15, 2nd line)</td>
<td>Doc 25 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>30%</td>
</tr>
<tr>
<td>Knez et al 2004</td>
<td>21</td>
<td>Doc 22 mg/m² d1, d8 4w with T 1 mg/m² q2w</td>
<td>21%</td>
</tr>
<tr>
<td>Rando et al 2004</td>
<td>17 (15 eval)</td>
<td>Doc 22 mg/m² d1, d8 4w with T 1 mg/m² q2w</td>
<td>39%</td>
</tr>
<tr>
<td>Raman per et al 2004</td>
<td>27 (25, 2nd line)</td>
<td>Doc 15 mg/m² d1, d8 4w with 8 10 mg/m² d1, d8 4w</td>
<td>31%</td>
</tr>
<tr>
<td>Ghio et al 2006</td>
<td>43</td>
<td>NAVICAP 4 cycles versus NAVICAP 4 cycles + Doc q2w</td>
<td>Overall 45% after first 3 cycles of NAVICAP, Not yet available</td>
</tr>
<tr>
<td>Passo et al 2008</td>
<td>61</td>
<td>Doc 20 mg/m² d1, d8 2w with VNR 13/15 mg/m² q2w with T 2 mg/m² q2w</td>
<td>67%</td>
</tr>
<tr>
<td>Rosati et al 2008</td>
<td>10</td>
<td>Doc 20 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>Overall 72%</td>
</tr>
<tr>
<td>(All 1st line)</td>
<td></td>
<td>Doc 20 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>Overall 72%</td>
</tr>
<tr>
<td>Waterhouse et al 2008</td>
<td>23</td>
<td>Doc 20 mg/m² q2w + Cap 600 mg/m² d1-2 q2w</td>
<td>25% (18 evaluable pts)</td>
</tr>
</tbody>
</table>

Days 1, 2, 8, 15, and 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 doxorubicin 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 (33.3%) 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 sepsis 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 (Palmieri et al. 2005). At least 1 visceral site of metastases 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.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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. Grade 3/4 neutropenia occurred in 8 patients (14%). Regarding non-hematologic toxicity, G3 adverse events were 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 10 patients with MBC (Mrozak 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 (12%), nausea/vomiting (13%), stomatitis (13%), and hand-foot syndrome (10%); among the hematologic 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 (Esteve 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% (6% 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 (Todesco et al. 2004). ORR was 50%. With regard to HER-2+ patients, the reported ORR was 63%, compared with a 14% response rate for HER-2-2 patients (p = 0.07). Patients with HER-2-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: weekly in group IA, 33 mg/m²; weekly on 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 IA and 8 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 epirubicin 30 mg/m²/week and docetaxel 35 mg/m²/week for 6 weeks with 1-week rest 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 (Ramondi et al. 2006). ORR was 12%, 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/d, l), and capecitabine (825 mg/m² bid d1–14) (NAVCAP)
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

**APPENDIX**

Weekly doxorubicin and metastatic breast cancer:

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 NAVECAP 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 enzyme 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 tarcezumab, 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 tarcezumab (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 38.1 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 III 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-polyglutamated liposomal anthracycline. DLT was 50 mg/m² and 30 mg/m² for paclitaxel and docetaxel respectively, combined with 25 mg/m² of non-polyglutamated liposomal anthracycline. A phase II trial followed and 48 patients were enrolled. The reported ORR was 72% (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-polyglutamated liposomal anthracycline is well tolerated and clinical benefit data encourage a phase III trial design.

The association between weekly docetaxel and vinorelbine 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 evaluate 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 an 8-week cycle. At the time of the analysis 112 patients were evaluable. TTP was the main endpoint of the study: 81 days
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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Table 5 Phase III trials

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>N. of pts</th>
<th>Regimen</th>
<th>TTP (months)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plater et al 2004</td>
<td>35</td>
<td>Doc 25 mg/m² q 3 w vs VHR 20 mg/m² q 3 w vs VHR 20 mg/m² q 6 w</td>
<td>2.7 versus 2.4</td>
<td>Not reported</td>
<td>9.4 months versus 8.42 months</td>
</tr>
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<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
</tr>
<tr>
<td>Burstein et al 2007</td>
<td>40</td>
<td>Doc 25 mg/m² q 3 w or P 80 mg/m² q 3 w or VHR T 25 mg/m² q 3 w vs VHR T 25 mg/m² q 3 w vs VHR T 25 mg/m² q 6 w</td>
<td>4 versus 6.5</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
<td>(6x)</td>
</tr>
<tr>
<td>Rivers et al 2002</td>
<td>39</td>
<td>Doc 75 mg/m² q 4 w or 1 1/2 w or Doc 25 mg/m² q 1 1/2 w or 28</td>
<td>Not reported</td>
<td>3.7 months versus 12.3 months</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Abbreviations: Doc, docetaxel; P, paclitaxel; VNR, vinorelbine; TTP, time to progression; OS, overall survival; q, every; Doc, docetaxel; VHR, vinorelbine.

(CT: 67-99) versus 103 days (CT: 98-119) were registered for vinorelbine versus docetaxel (p = 0.1178). OS was 253 (CT: 173-331) versus 258 days (CT: 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, anaemia 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 hyperbilirubinemia. 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 3.5 months, 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
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
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APPENDIX

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

Cristina Raimondi¹, Marco Danova², Sofia Chatziileontiadou², Laura Palmeri¹, Alessandro Vercelli³, Sergio Palmeri¹

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 chirurgia o chemioterapia è di 6-14 mesi. Negli ultimi anni, nuovi regimi di chemioterapia e la terapia molecolare mirata 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 selezionati. 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'efficacia della resezione epatica e dell'ablazione a radiofrequenza sulla cura 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 chirurgici; in genere, essi dovrebbero essere considerati trattamenti di riduzione, e non tutti, necessitano 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 oncologist 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 or 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.

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APPENDIX


La riduzione del volume tumorale totale fino a dimensioni che ne consentano il trattamento dimi-
nuisce sostanzialmente la possibilità che le cellule tumorali sviluppinofarmacoresistenza, configuran-
dosi quale utile aggiunta alla terapia sistemica nel migliorare i risultati. Le indicazioni al trattamento chirurgico sono controverso (tabella 2), ma i risultati mostrano che metastasi stabilis possano essere russe-
cale con successo. Lo sviluppo di chemioterapia e le terapie molecolari target, insieme con nu-
ove modalità come l’ablazione a radiofrequenza, più af-
finate tecniche di imaging presessoriteriali e migliorati ri-
sultati operatori hanno ottenuto le evidenze per la resezione epatica e migliorato la sopravvivenza. Inol-
tro, i percentuali di mortalità operatoria sono co-
stantemente ridotte a meno del 5%, con un’accettabile morbilità.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
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APPENDIX

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PC regimen</th>
<th>GA regimen</th>
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<tbody>
<tr>
<td>Eligible patients</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td>Males</td>
<td>46</td>
<td>35</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>30</td>
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<tr>
<td>Median age (range) years</td>
<td>64 (44-79)</td>
<td>64 (48-76)</td>
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<tr>
<td>Aged-70 years</td>
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<td>Charlson score 3</td>
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<tr>
<td>Cancer score 3</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>Unspecified</td>
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<tr>
<td>Recurrent disease</td>
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<td>Infection</td>
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</tr>
<tr>
<td>Median length</td>
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<td>13</td>
</tr>
</tbody>
</table>

Patients (41%) were affected by adenocarcinoma, and 59% of them had a metastatic disease.

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 PC arm. Similar proportions of patients in the two arms received 4 or 6 cycles of treatment.

In the GA arm, 9% of doses were reduced, and 14% were omitted, the PC arm, 14% of doses were reduced, and 5% were omitted.

3.3. Activity

In the GA arm, 35 (confirmed) patients were registered, for 108 (105). In the PC arm, patients achieved a partial response, which was confirmed in 17 cases. Therefore, the RR was 32% (95% CI, 26-46%). Comparative proportions of patients achieved a stable disease or showed progression during treatment, while a greater number of patients in the PC arm were not assessed for response because of early clinical deterioration (Table 3).

Table 3: Treatment disposition according to regimen on study.

<table>
<thead>
<tr>
<th>Treatment disposition</th>
<th>PC regimen</th>
<th>GA regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivered cycles</td>
<td>228</td>
<td>198</td>
</tr>
<tr>
<td>Median number of cycles/patient range</td>
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<td>5-6</td>
</tr>
<tr>
<td>Patients treated with</td>
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<td>25%</td>
</tr>
<tr>
<td>2 cycles</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>4 cycles</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>6 cycles</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

3.4. Toxicity

Acute toxicity of the two regimens is reported in Table 3. The most common severe hematologic toxicity of the GA regimen was neutropenia (30%, and febrile neutropenia (14%). Other events were febrile neutropenia (10%), diarrhea (16%), and fatigue (3%).
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

Table 3

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>NC 1</th>
<th>NC 2</th>
<th>NC 3</th>
<th>NC 4</th>
<th>AA 1</th>
<th>AA 2</th>
<th>AA 3</th>
<th>AA 4</th>
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<tr>
<td>Anemia</td>
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<tr>
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<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>Hair loss</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>Nausea</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Diarrhea</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Mucositis</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

3.5. Quality of life

Baseline quality of life questionnaires were available for 100 of 105 patients: 47 (92%) patients in the CA arm, and 53 (96%) patients in the PC arm. Excluding a non-significantly greater pain score registered in the CA 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 CA arm, and 56 (range, 0–100) in the PC arm. After three courses, questionnaires were available for 29 (57%) patients in the CA arm, and for 37 (69%) patients in the PC arm. Excluding a significantly (P < 0.001) worse score for the subjective perception of peripheral neuropathy and hair loss in the PC arm, no other differences 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 CA arm, second-line chemotherapy consisted of docetaxel, alone (eight cases) or combined with CDDP or CRDCA (two cases), or PTX plus GEM (one case). Eight patients received erlotinib in second (four cases), or third line (four cases). In the PC arm, seven patients received second-line pemtredonir, alone (six cases), or with CRDCA (one case), and four received docetaxel with CDDP. Eight patients were treated with erlotinib.

3.7. DFS 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 DFS curves are plotted in Fig. 1. Median DFS was 5.1 (95% CI, 3.7–6.5) months in the CA arm, and 3.3 (95% CI, 1.9–6.2) months in the PC arm (HR, 1.48 [95% CI, 1.20–1.81], P = 0.004). Fig. 2 shows the OS curves: 1-year survival probability was 42% in the CA arm, and 58% in the PC arm; 2-year survival probability was 21% for both PC arm, while no patient survived beyond 2 years in the CA arm. Median OS was 10.5 (95% CI, 7.3–13.5) months for CA arm, and 12.3 (95% CI, 11.7–14.9) months for PC arm (HR, 1.29 [95% CI, 1.04–1.61], P = 0.018). A similar difference in favor of PC treatment was observed comparing OS of patients with non-squamous histology.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

APPENDIX
Casi clinici in oncologia

1 messaggio

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A. Laura Palmeri@gmail.com

Egregio Dottore,

Siamo lieti di comunicarle che, a seguito dell'accettazione del suo caso clinico, le verrà riconosciuto un compenso lordo di euro 1.000.
Il suo caso sarà inserito nel nostro volume numero 34.
In allegato la invito a compilare e rendere, per qualsiasi informazione non esita a chiamarmi.
Cordiali saluti.

Nicoletta Mottini - Ufficio Amministrazione - Med Stage srl
Tel 02 91764491; Fax 02 9176438
Via di Vittoria, 9 - 20165 lezago (Milano)

2 allegati

med stage, pastedGraphic.png
14K

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126K
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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
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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 studio III, correlata all’infezione da HBV. Nel mese di febbraio ricorreva all’ospedalizzazione, in reparto di nefrologia, per stato anasarca, 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 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 collateralori perisplenici, perigastrici e mesenterici; vari contesti esofagei; 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 +, Sinaptosfisina +, 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.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

APPENDIX

**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/m² 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 febrile 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/m²) 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.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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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.


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, cosicché 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...
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

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

BIBLIOGRAFIA

Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.

APPENDIX

Treating non-hepatic cancer in cirrhotic patients

caldeiras et al.

Cirrhosis is highly variable, being influenced by a number of factors, including disease stage, aetiology and duration of the disease. The use 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 is crucial to evaluate the tumour and the patient characteristics (e.g., chemosensitivity, site of disease, kind and degree of symptoms), as suggested by the experience with hepatocellular carcinoma (HCC) patients treated with sunitinib (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 unsolved 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 are activated if they are pro-drugs. Hence, there are potential hazards in the administration of anti-cancer therapy to patients with an abnormal liver.

![Diagram](https://example.com/diagram.png)

Fig. 1. Proposed decision algorithm for patients with cirrhosis and non-hepatic cancer.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.
Cisplatin (C) and (A) with panitumumab for advanced non-squamous non-small cell Lung cancer (NS-NSCLC): a phase I-Dose finding study.