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Carcinoma dello stomaco e terapia di mantenimento

Il carcinoma gastrico e la terapia di mantenimento

- **Caratteristiche cliniche dei pazienti (sedi metastatiche difficili, rapido deterioramento delle condizioni generali,..)**
- **Risultati deludenti nella malattia metastatica (PFS, OS)**
- **Difficoltà a definire lo standard terapeutico di prima linea se non per i tumori HER-2 (<20%)**
- **Ruolo della seconda linea**

Il carcinoma gastrico e la terapia di mantenimento

- **A favore**
  - **Buona percentuale di risposte obiettive e/o di stabilizzazioni cliniche ma di breve durata**
  - **Differenza minima fra PFS (coincide quasi con la durata della terapia) e OS**
  - **Disponibilità di agenti biologici più tollerabili dei chemioterapici**
- **A sfavore**
  - **Tossicità cumulativa o induzione di resistenza per molti dei farmaci attivi (analoghi del platino, antracicline, fluoropirimidine,..)**
  - **Pazienti spesso anziani che tollerano male lunghi trattamenti**
  - **Possibilità di avere II° linee efficaci**

Buona percentuale di risposte obiettive e/o di stabilizzazioni cliniche ma di breve durata

Regimen	RR	duration	Source
ECF	45%	6 mo	JCO 1997
	42%	5 mo	JCO 2002
TCF	37%	5 mo	JCO 2006

Differenza minima fra PFS (coincide quasi con la durata della terapia) e OS

Regimen	RR	TTP	Median OS	Source
CF	25%	3.7 mo	8.6 mo	ASCO 2005
	26%	4.2 mo	8.7 mo	ASCO 2005
ECF	45%	7.4 mo	8.9 mo	JCO 1997
	42%	7.0 mo	9.4 mo	JCO 2002
IF	32%	5.0 mo	9.0 mo	ASCO 2005
TCF	37%	5.6 mo	9.2 mo	JCO 2006

Disponibilità di agenti biologici più tollerabili dei chemioterapici

- **Trastuzumab**
- **Bevacizumab**
- **Everolimus**
- **Marimastat**

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Marimastat as maintenance therapy for patients with advanced gastric cancer: a randomised trial

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This randomised, double-blind, placebo-controlled study was designed to evaluate the ability of the orally administered matrix metalloproteinase inhibitor, marimastat, to prolong survival in patients with non-resectable gastric and gastro-oesophageal adenocarcinoma. Three hundred and sixty-nine patients with histological proof of adenocarcinoma, who had received no more than a single regimen of 5-fluorouracil-based chemotherapy, were randomised to receive either marimastat (10 mg b.d.) or placebo. Patients were treated for as long as was tolerable. The primary endpoint was overall survival with secondary endpoints of time to disease progression and quality of life. At the point of protocol-defined study completion (85% mortality in the placebo arm), there was a modest difference in survival in the intention-to-treat population in favour of marimastat (P=0.07 log-rank test, hazard ratio=1.23 (95% confidence interval 0.98–1.55)). This survival benefit was maintained over a further 2 years of follow-up (P=0.024, hazard ratio=1.27 (1.03–1.57)). The median survival was 138 days for placebo and 160 days for marimastat, with 2-year survival of 3% and 9% respectively. A significant survival benefit was identified at study completion in the pre-defined sub-group of 123 patients who had received prior chemotherapy (P=0.045, hazard ratio=1.63 (1.00–2.34)). This benefit increased with 2 years additional follow-up (P=0.006, hazard ratio=1.68 (1.16–2.44)), with 2-year survival of 6% and 18% respectively. Progression-free survival was also significantly longer in the marimastat treated patients compared to placebo (P=0.009, hazard ratio=1.32 (1.07–1.63)). Marimastat treatment was associated with the development of musculoskeletal pain and inflammation, events of anaemia, abdominal pain, jaundice and weight loss were more common in the placebo arm. This is one of the first studies of therapeutic benefit for a matrix metalloproteinase inhibitor in cancer patients. The greatest benefit was observed in patients who had previously received chemotherapy. A further randomised study of marimastat in these patients is warranted.

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Gastric cancer is the fourth most common cause of cancer death in Europe with an incidence of 24 per 10^4 population in males and 16 per 10^4 population in females (Stadtlander and Waterborg, 1999). Even in the US, where there has been a sharp decline in the incidence of gastric cancer over the past 50 years, the incidence of adenocarcinoma of the gastro-oesophageal junction has increased rapidly (Devesa et al, 1998).

Gastric cancer spreads by local extension to form lymphatic, peritoneal and distant metastases. As a result of early spread, only 10–20% of patients present with resectable disease. For the remainder, surgical debulking will be attempted in some while others will be considered inoperable. Until recently there has been relatively little evidence of a survival benefit for established cancer therapies in this disease, however results from a recent US study have shown a significant survival benefit for the use of adjuvant 5-fluorouracil (5-FU) and radiation in patients following curative resection (Macdonald et al, 2001) and a meta-analysis of the available randomised evidence also supports the use of adjuvant chemotherapy following curative resection (Mari et al, 2000).

In patients with inoperable gastric cancer, the data regarding the use of chemotherapy are less clear. A survival benefit has been shown for fine regimen vs best supportive care (Glimelius et al, 1996; Ajani et al, 1998; Rath et al, 1999; Wagner et al, 1999; Chao et al, 2000) and in a small number of studies with small numbers of patients comparing chemotherapy with best supportive care (Murad et al, 1993; Pyrhonen et al, 1995; Glimelius et al, 1997). The absence of a large randomised study of chemotherapy vs best supportive care has allowed the debate on its merits to continue. As a result a wide range of 5-FU based chemotherapy regimens are offered to patients and a proportion of patients are offered no cytotoxic therapy at all. Recent changes in attitude towards the non-operative management of solid gastrointestinal tumours have led to a renewed interest in the development of novel agents that exploit increasing knowledge of the molecular and cellular biology of malignancy. Matrix metalloproteinase inhibitors are designed to target particular pathways with synthetic compounds and inhibit these pathways for potential therapeutic benefit. Several of these strategies have been tested in clinical trials in patients with a variety of tumour

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survival difference in favour of marimastat was maintained with a further 2 years of follow-up (ITT, P=0.024 log-rank test, HR=1.27 (1.03–1.57)), with median survival times of 160 days for marimastat and 138 days for placebo, and 2-year survival of 9% and 3% respectively (Figure 1). The modified ITT analysis showed a marginally greater survival benefit (P=0.014 log rank test, HR=1.30 (1.05–1.61)) for result after 2 years of additional follow-up.

Analysis of overall survival in the predefined sub-group of patients who had received prior chemotherapy revealed a significant benefit for marimastat at the primary analysis point (P=0.045 log-rank test, HR=1.63 (1.00–2.34)). This survival difference increased with 2 years of additional follow-up (P=0.006 log-rank test, HR=1.68 (1.16–2.44)), with median survival times of 253 days for marimastat and 175 days for placebo, and 2-year survival of 18% and 5% respectively (Figure 2). Importantly, there was no evidence of an adverse effect on survival in the patients who had not received chemotherapy (P=0.515 log-rank test, HR=1.09 (0.84–1.40)).

There was also a significant benefit in progression-free survival at the primary analysis point (P=0.014 log-rank test, HR=1.31 (1.05–1.63)). This difference was maintained over the 2 years of additional follow-up (P=0.009 log-rank test, HR=1.32 (1.07–1.63)) (Figure 3).

The possibility of bias or imbalance between the arms was explored as an explanation for the survival differences. Interactions between several factors precluded a single multifactorial analysis to adjust for baseline prognostic factors. There was a small imbalance in ECOG status in the ITT population with 70% of placebo patients having a status of 1 vs 64% of marimastat patients. Other baseline prognostic factors were well balanced for the ITT population. The chemotherapy sub-group was found to have minor imbalances in favour of marimastat for ECOG status (ECOG 1 57% vs 63% for marimastat and placebo respectively), and in favour of placebo for metastases (M1 72% vs 68%) and no prior resection (74% vs 65%). Another source of imbalance was recruitment of three placebo patients and six marimastat patients who had resectable disease (T1-2, N0-1). The chemotherapy sub-group contained one patient with resectable disease in each arm. When these patients were excluded, the overall survival benefit after 2 years additional follow-up was reduced and only just significant (P=0.049 log-rank test, HR=1.24 (1.00–1.53)). However, the result for the chemotherapy sub-group was largely unchanged (P=0.010 log rank test, HR=1.63 (1.12–2.37)).

The robustness of the survival benefit in the chemotherapy sub-group was confirmed further by regression analyses to account for individual prognostic factor imbalance. None of the factors diminished the hazard ratio below 1.61, and the imbalance in prior surgical debulking increased the hazard ratio to 1.77. Furthermore, when divided in two halves on the basis of recruitment period, a survival trend in favour of marimastat is seen in both halves (HR=1.51 and HR=2.04).

Quality of life analyses using the EORTC-QLQC30 instrument were performed at baseline, 6 weeks, 12 weeks and at 3-monthly intervals thereafter. There was no statistically significant difference between placebo and marimastat in standardised area under the curve (AUC) (mean 57.9 vs 56.5, P=0.49) or change from baseline standardised AUC (mean 7.0.87 vs 7.3.82, P=0.18) over the first 12 weeks of the study (Wilcoxon rank-sum tests). Further analysis was prevented by a marked reduction in the number of patients remaining on study and able to complete the questionnaire.

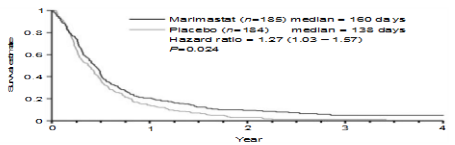

Figure 1 Overall survival (intention to treat).

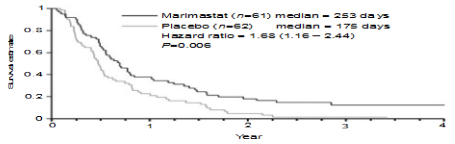

Figure 2 Overall survival (Chemotherapy sub-group).

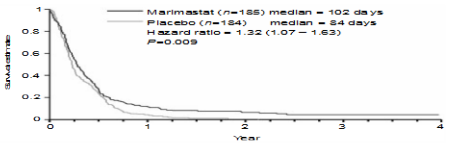

Figure 3 Progression-free survival (intention to treat).

Table 3 NCI-CTC graded adverse events (all causalities)

	Placebo		Marimastat	
Adverse event (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Vomiting	32.6	5.5	30.7	5.0
Constipation	30.9	5.5	27.9	7.3
Nausea	30.4	4.4	28.5	5.0
Musculoskeletal pain	22.7	0.6	43.6	12.8
Neuro: cortical	22.7	10.5	33.5	12.3
Weight gain/loss	22.7	2.8	15.6	1.1
Infection	17.1	3.9	17.3	6.1
Diarrhoea	15.5	1.1	14.5	2.2
Neuro: motor	15.5	7.1	11.2	7.8
Haemorrhage	9.9	3.9	10.1	3.4
Skin	9.4	2.8	13.4	1.1
Neuro: sensory	9.4	0.6	8.4	0
Pulmonary	8.8	9.9	11.7	7.3
Fever	6.6	0	4.4	1.7

Tossicità cumulativa di molti farmaci attivi (analoghi del platino, antracicline, fluoropirimidine,..)

- **Cisplatino**
- **Oxaliplatino**
- **Antracicline**
- **fluoropirimidine**

Possibilità di avere II° linee efficaci

- **Il 30-50% dei pazienti riceve una seconda linea che impatta sulla sopravvivenza**
- **La stabilità ha una durata breve. Per questi pazienti conviene pensare ad un cambio precoce di terapia**

Trials attivi

- **Taxanes or Platinum in Combination With Capecitabine Followed by Capecitabine Alone as First Line Treatment for Patients With Advanced Adenocarcinoma of Stomach or Esophagogastric Junction**

Chau, Poster Discussion