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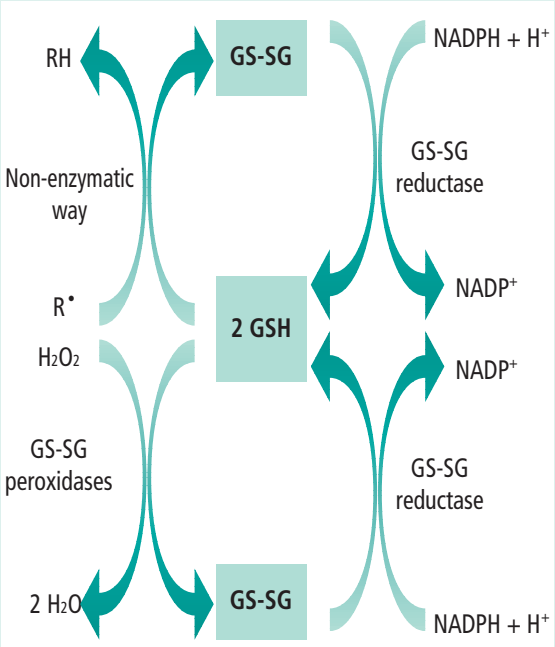
Role of glutathione

Glutathione is a physiological tripeptide, composed of glutamic acid, cysteine and glycine, ubiquitous in eukaryotic cells where it represents the largest reservoir of non-protein thiol groups reaching concentrations ranging from 0.5 to 10 mM. In humans, the organs with the highest levels of glutathione are the liver, the crystalline lens of the eye, the kidneys, the pancreas and the spleen.

Glutathione is considered an essential component for maintaining cellular homeostasis: it actually intervenes directly or indirectly in several biological processes such as the synthesis of proteins and nucleic acids, the transport of amino acids, maintaining enzymes in active form and the integrity of cellular membranes. In addition to representing a reserve of cysteine, glutathione plays an extremely important role in detoxification reactions, protecting cells from the action of xenobiotic, environmental oxidant (hyperoxia, hyperbaric oxygen, ozone) and intracellular (free radicals, reactive oxygen intermediates) and radiation agents.

Glutathione exists in two forms, the reduced form (GSH) and the oxidised form (GS-SG) bound by a disulphide bond between the two cysteine residues. It is the reduced form that intervenes in detoxification processes in two ways: a non-enzymatic and a enzymatic way (Fig. 1).

Figure 1. *GSH: role in detoxification processes (from: Exner R et al. Wien Klin Wochenschr 2000;112(14):610; mod.).*



Since GSH can perform its intracellular action, the role of a family of enzymes is important: the glutathione-S-transferase (G-ST) that catalyses the conjugation of GSH with many endogenous and exogenous substrates.
G-STs are especially present in hepatocytes, erythrocytes and intestinal cells; they catalyse the conjugation of GSH with exogenous and endogenous compounds such as, for example, the products of lipid peroxidation and free radicals.
During oxidative stress highly reactive intermediates are formed, such as hydrogen peroxide and superoxides that promote the production of oxygen radicals which, in turn, damage cellular membranes.
In this regard, it is necessary to say that GSH is the most powerful intracellular antioxidant.
Maintaining the intracellular homeostasis of the glutathione system provides the right balance between synthesis, degradation, oxidation-reduction and conjugation with various electrophile substrates and an adequate transport speed inside and outside the cells of the amino acid precursors. This balance is less when tissues are exposed to drugs (such as paracetamol, chemotherapy), alcohol, ionising radiation and events that lead to a reduction in concentrations of glutathione; the consequent depletion of GSH harms cells' ability to defend themselves, resulting in damage or cell death.
The exogenous administration of GSH can compensate for this loss, allowing the protective detoxification mechanisms to be restored. Glutathione is not transported as such in cells and therefore the way in which exogenous GSH is capable of increasing the intracellular concentrations of endogenous peptide is its hydrolysis by the work of the enzyme γ-glutamyl transpeptidase, to aminoacidic precursors, which are immediately transported into cells where they serve as substrates for the new synthesis of GSH. Consequently, the exogenous administration of GSH increases tissue levels of GSH providing the building blocks for an "ex-novo" synthesis.
It has been noted that many chemotherapy treatments, including cisplatin and similar, reduce tissue and intracellular levels of endogenous GSH, aggravating the condition of oxidative stress induced by the tumour.
One of the main problems of treatment with cisplatin and oxaliplatin is represented by neurotoxicity, which manifests itself as peripheral neuropathy.
The latter represents the cumulative predominant toxicity of cisplatin and oxaliplatin, which occurs mainly after the administration of the overall doses of cisplatin >300 mg/m^2 and, respectively, of oxaliplatin >800 mg/m^2.
The prerequisite rationale for the clinical use of exogenous GSH as an adjuvant in the treatment of neurotoxicity by cisplatin and oxaliplatin is basically based on the evidence that platinum derivatives have a high affinity with nucleophile compounds which contain SH groups, such as GSH. GSH can therefore become an alternative target for reactive intermediates of cisplatin and similar ones, by removing and deactivating them.
Exogenous GSH is not able to cross over by spread the cell membranes, but it only penetrates tissue cells that have a high expression of the enzyme γ-glutamyl transpeptidase, assigned to the hydrolysis of GSH in its amino acid components. The selectivity of the cytoprotective action of exogenous GSH on healthy tissue may be related to its limited penetration in tumour cells due to the reduced levels of γ-glutamyl transpeptidase found in them.

Conclusions

GSH is a relatively simple molecule, but capable of performing several important functions; it plays a crucial role in protecting the intracellular environment from oxidative stress in detoxification processes and maintaining the integrity of the cell membrane.
There are several conditions that lead to depletion of GSH (paracetamol, chemotherapy for cancers, alcohol, ionising radiation) with consequent damage or cell death.
In these situations, the administration of exogenous GSH can compensate for this loss, allowing the integrity of cellular membranes and protective detoxification mechanisms to be restores.

Glutathione reduces toxicity and improves the quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised study

J.F. Smyth, M. Tedeschi

Extract from Annals of Oncology 1997;8:569-573

Introduction

Ovarian cancer is the fifth most common female cancer in the UK.

Cisplatin (CDDP) is one of the most effective medicinal products for treating ovarian cancer.

The standard dose of CDDP is 100 mg/m^2 every 3 weeks for 6 treatment cycles. Often neurotoxicity, which already appears in the cumulative dose of 300 mg/m^2 of CDDP, represents a factor limiting the treatment.

Objectives

The objective of this clinical study was to assess the effect of reduced glutathione (GSH) on the toxicity of CDDP and on quality of life.

Type of study

Multicentric, randomised, double-blind, placebo-controlled study.

Materials and methods

- Number of patients: 151 with ovarian cancer, stage I-IV.
- Placebo group (n=77): CDDP 100 mg/m^2, every 3 weeks x 6 cycles.
- GSH group (n=74): CDDP 100 mg/m^2, every 3 weeks x 6 cycles + GSH 3 g/m^2 by infusion in the 20 minutes before the administration of CDDP.

Results

- Treatment with GSH increases, in a statistically significant way, the percentage of patients who completed the 6 cycles of therapy, compared with the placebo group (58% vs 39% - p<0.05) (Fig. 1).
- Treatment with GSH tends to increase the percentage of complete or partial responses (74% vs. 62% p=n.s.): this shows that GSH does not interfere with the antitumour efficacy of CDDP (Fig. 2).

Figure 1. *Patients who completed 6 cycles of therapy.*

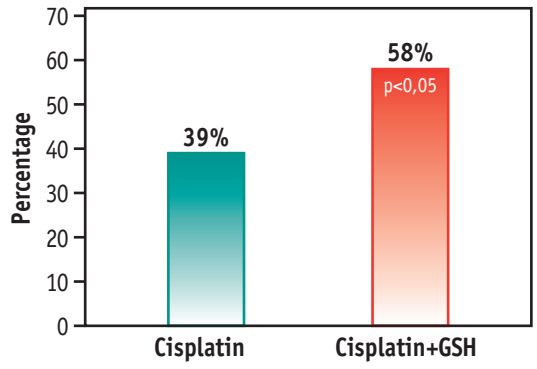
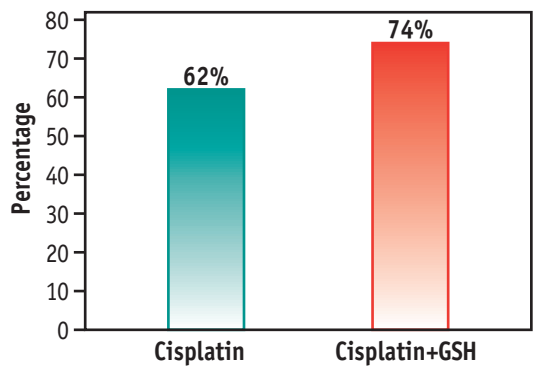


Figure 2. *Complete or partial response.*



- Treatment with GSH reduces the toxicity of CDDP and significantly improves quality of life. In particular, the following parameters showed a statistically significant improvement: depression, nausea, vomiting, tingling of the hands and feet, hair loss, shortness of breath, difficulty concentrating, managing housekeeping tasks and shopping.

Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomised, double-blind, placebo-controlled study

S. Cascinu, G. Catalano

Extract from the Journal of Clinical Oncology 1995;13:26-32

Introduction

Cisplatin (CDDP) is a very effective chemotherapy and widely used alone or in combination in many malignant tumours.

Nephrotoxicity and neurotoxicity are the most significant side effects of CDDP.

While nephrotoxicity can be exceeded by over hydration and diuretics, neurotoxicity remains the main side effect.

Objectives

The objective of this clinical study was to assess the efficacy of reduced glutathione (GSH) to prevent the neurotoxicity of cisplatin.

Type of study

Randomised, double-blind, placebo-controlled study.

Materials and methods

- Number of patients: 50 with advanced gastric cancer (stage III-IV).
- Placebo group (n=25): CDDP 40 mg/m^2 + 5-fluorouracil 500 mg/m^2 + 4 epidoxorubicin 35 mg/m^2 + leucovorin 250 mg/m^2, every week for 9-15 weeks.
- GSH group (n=25): treatment for placebo group + GSH 1.5 g/m^2 by infusion in the 15 minutes before the administration of CDDP. GSH 600 mg IM on days 2 and 5.
- Assessment parameters: complete neurological clinical examination acc. to WHO; electrophysiological examination of the nerves: median, ulnar and sural (latency and sensory amplitude potential).

Results

Treatment with GSH reduces the incidence of neuropathy grade II-IV (Fig. 1).

In particular after 9 weeks of treatment, no GSH patient group showed neuropathy grade II-IV, compared to 16% in the placebo group (p=0.0001).

After 15 weeks of treatment, the incidence of neuropathy from grade II-IV and 4.2% in the GSH group, compared to 72.2% in the placebo group (relative reduction of 94.2%; p=0.0001).

Moreover, even in those few patients in the GSH group who developed neuropathy, this was less serious (score=0.2 vs 1.83 placebo group; p<0.0001).

Also the electrophysiological assessment demonstrated a protective effect of GSH: while in the placebo group there was a statistically significant deterioration of the mean latency and sensory amplitude potential, these parameters did not significantly change in the GSH group (Tab. I).

This shows that GSH protects the functionality of peripheral nerves, reduced by cisplatin.

The antitumour efficacy of cisplatin is maintained, and indeed there was a trend toward a better response: in the GSH group there was complete clinical remission in 20% of patients, partial remission in 56% and an overall response in 76%, while in the placebo group the results were, respectively, 12%, 40% and 52%.

Figure 1. *Incidence (%) of neuropathy grade II-IV and score (grade I-IV).*

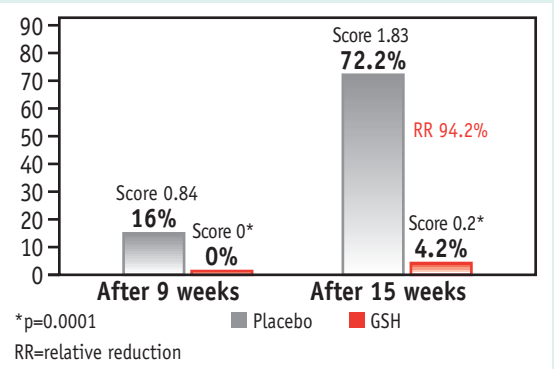


Table I. *Electrophysical assessment.*

	Placebo			GSH		
	Median nerve	Ulnar nerve	Sural nerve	Median nerve	Ulnar nerve	Sural nerve
Latency (ms)	Statistically significant increase in the 15th week			No statistically significant variation		
Amplitude (μV)	Statistically significant increase in the 9th and in the 15th week			No statistically significant variation		

Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomised, double-blind, placebo-controlled study

S. Cascinu, G. Catalano

Extract from the Journal of Clinical Oncology 2002;20:3478-3483

Introduction

Oxaliplatin, in combination with 5-fluorouracil, represents an effective 1st line cancer treatment for colorectal cancer but very often causes peripheral sensory neuropathy when the cumulative dose approximates to 800 mg/m^2.

Objectives

The objective of this clinical study was to assess the efficacy of reduced glutathione (GSH) to prevent neurotoxicity from oxaliplatin.

Type of study

Randomised, double-blind, placebo-controlled study.

Materials and methods

- Number of patients: 52 with advanced colorectal cancer.
- Placebo group (n=26) on day 1: oxaliplatin 100 mg/m^2 + leucovorin 250 mg/m^2 + 5-fluorouracil 1500 mg/m^2 (for 2 days), every 2 weeks for 12 cycles.
- GSH group (n=26): placebo group treatment + GSH 1.5 g/m^2 by infusion in the 15 minutes before the administration of oxaliplatin.
- Assessment parameters: complete neurological clinical examination acc. to WHO; electrophysiological examination on sural nerve (latency and sensory amplitude potential and conduction velocity).

Results

Treatment with GSH reduced by 83.6% and 70%, respectively after 8 and 12 cycles of treatment, the incidence of neuropathy grade II-IV (Fig. 1).

Also the scores were significantly lower, demonstrating that in the GSH group neuropathy, even when manifested, was much less severe (Fig. 1).

The electrophysiological assessment demonstrated that GSH protects the functionality of peripheral nerves, reduced by oxaliplatin (Tab. I).

The antitumour efficacy of oxaliplatin was maintained: the response percentage was 26.9% in the GSH group and 23.1% in the placebo group.

Figure 1. *Incidence (%) of neuropathy from grade II-IV and score (grade I-IV).*

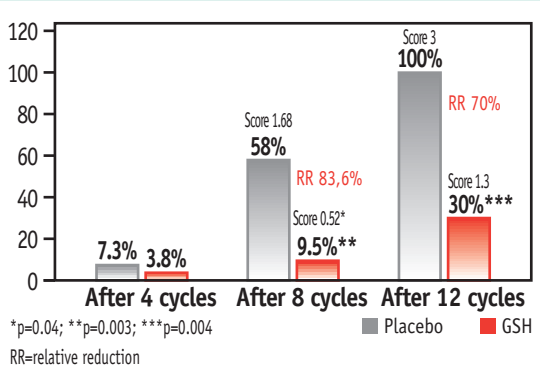


Table I. *Electrophysiological assessment after 8 cycles.*

Sural nerve	Placebo	GSH
Latency (ms)	Statistically significant increase	No statistically significant variation
Amplitude (μV)	Statistically significant increase	No statistically significant variation
Conduction velocity (m/sec)	Statistically significant increase	No statistically significant variation

High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione and filgastrim in patients with locally advanced, unresectable gastric cancer: report by the Italian Group for the Study of Digestive Tract Cancer (GISCAD)

S. Cascinu, V. Franciosi

Extract from British Journal of Cancer 2004;90:1521-1525

Introduction

Although the incidence of gastric cancer is declining, it still represents one of the main causes of death associated with cancer.

Surgery remains the single most important curative treatment, but only when a radical resection is possible.

Patients that cannot be operated on generally receive chemotherapy to relieve the pain of the symptoms and to improve their quality of life.

Only a few studies have focused on the role of pre-operative chemotherapy in unresectable gastric cancer.

Objectives

The objective of this clinical study was to assess the effects of intensive weekly treatment in a group of patients with unresectable gastric cancer.

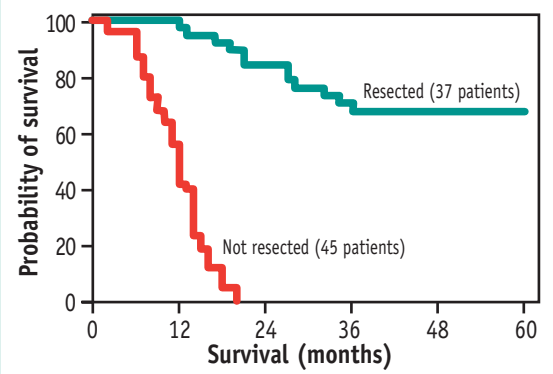
Type of study

Open multicentric study.

Materials and methods

- Number of patients: 82, with locally advanced, unresectable gastric cancer (tumour size >7 cm, invasion of adjacent structures, but without distant, liver and peritoneal metastases).
- Treatment: PELFw: GSH 1.5 g/m^2 by infusion in the 15 minutes before the administration of cisplatin 40 mg/m^2 + 5-fluorouracil 500 mg/m^2 + epidoxorubicin 35 mg/m^2 + 6S-leucovorin 250 mg/m^2 every week for 8 weeks. Between one cycle and another: filgastrim 5 µg/kg.
- Assessment parameters: percentage of objective responses (complete or partial), tolerability.

Figure 1. *Kaplan-Meier survival curves for patients who underwent curative resection of primitive gastric cancer after chemotherapy and unresected patients.*



Results

- Objective responses: 49% → complete: 7%; partial: 42%
- Stabilisation: 36%
- Progression: 15%

Of the 49% (n= 40) of patients with objective responses, 92.5% (n= 37) was able to undergo resectability surgery.

After a median follow-up period of 48 months, 68% of patients operated on were alive and 65% were disease free (Fig. 1). The median survival time was 12 months for unresectable patients, while the same was not achieved for operated patients after intensive chemotherapy treatment (Fig. 1).

The tolerability was generally good; in particular, no patients presented peripheral neuropathy grade III-IV, confirming the efficacy of GSH in preventing the neurotoxicity of cisplatin.

Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer (MOSAIC Study)

T. André, A. de Gramont (MOSAIC Investigators)

Extract from New England Journal of Medicine 2004;350:2343-2351

Introduction

Colorectal cancer is the second cause of death from cancer. About 40-50% of patients who undergo potentially curative surgery alone, relapse or die from metastatic disease.

Objectives

The objective of this clinical study was to assess the effect of an adjuvant treatment with fluorouracil and leucovorin with and without oxaliplatin, in patients with colon cancer.

Materials and methods

- Number of patients: 2,246 with colon cancer, stage II (T3 or T4, NO, MO) or stage III (any T, N1 or N2, MO).
- Placebo group (n=1,123): leucovorin 200 mg/m^2 + 5-fluorouracil 400 mg/m^2 in bolus + 600 mg/m^2 by infusion for 2 days, every 14 days, for 12 cycles.
- Oxaliplatin group (n=1,123): treatment of placebo group + oxaliplatin 85 mg/m^2, on day 1, every 14 days, for 12 cycles (cumulative dose oxaliplatin 1,020 mg/m^2).
- Assessment parameters: disease-free survival (DFS); overall survival; tolerability.

Results

Disease-free survival at 3 years (Fig. 1):

- placebo group 72.9%;
- oxaliplatin group 78.2%; p=0.002.

Events related to the tumour (relapses, deaths) (Fig. 1):

- placebo group 26.1%;
- oxaliplatin group 21.1%; p=0.002.

The risk of relapse in the oxaliplatin group was reduced by 23% (p=0.002).

As regards tolerability, the most frequently reported adverse event was sensory neuropathy.

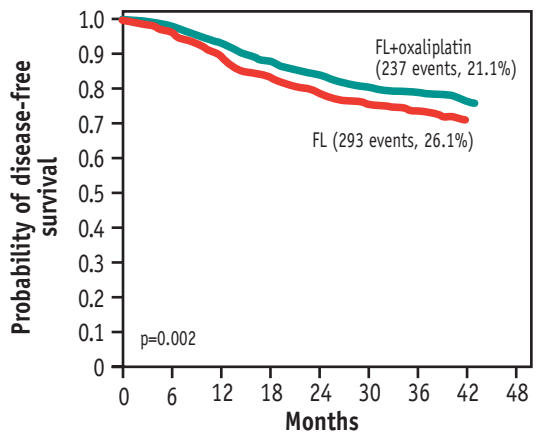
Considering grades I-III, the incidence was 92.2% and in 12.4% of the patients, the neuropathy was grade III.

Furthermore, while peripheral neuropathy of grade III was almost completely reversible in the 12 months of follow-up, that grade I-II persisted in 28.4% of patients.

Therefore, in the MOSAIC study the addition of oxaliplatin with the standard adjuvant treatment for colon cancer represented a therapeutic improvement but the resulting sensory neuropathy was the main problem.

To overcome this problem, the clinical studies described above demonstrated that GSH, in a dosage of 1.5 g/m^2 prevents neuropathy from cisplatin and oxaliplatin.

Figure 1. *Kaplan-Meier estimates of disease free survival in the group treated with fluorouracil and leucovorin (FL) and in the group treated with FL and oxaliplatin, according to the Intention to treat anlysis.*



N. at risk

FL+oxaliplatin	1,123	1,086	1,023	959	888	663	395
FL	1,123	1,066	981	903	817	619	356

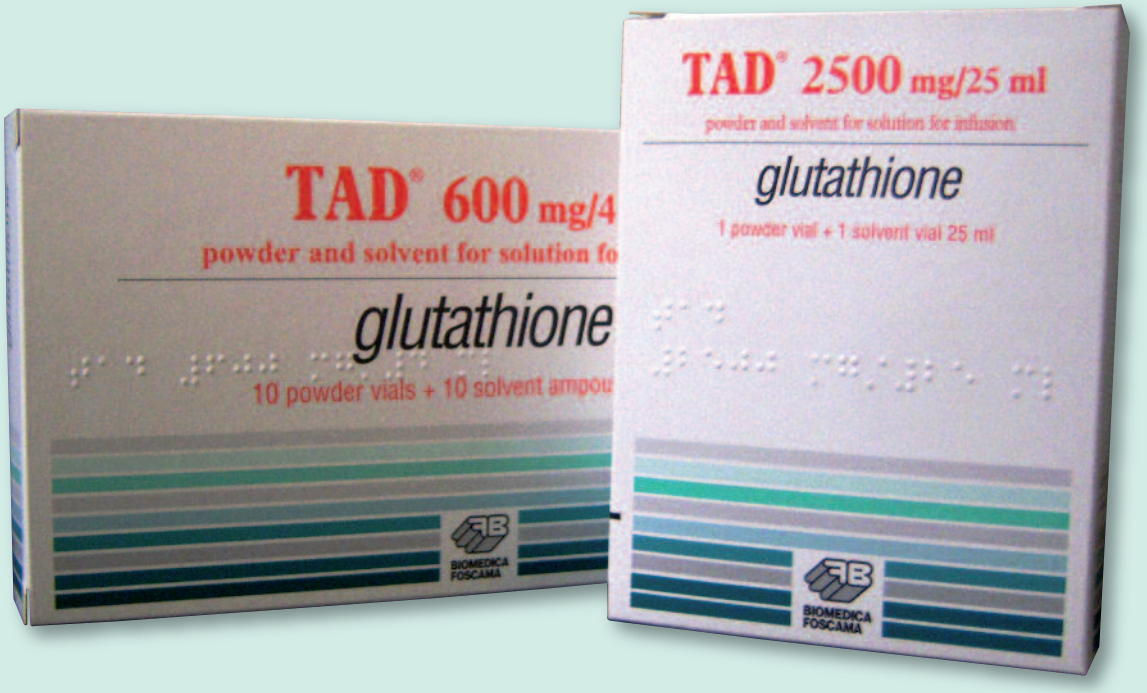
RR for relapse = 0.77: FL group + oxaliplatin vs FL group (IC 95% = 0.65-0.91; p=0.002)

TAD® 600 mg/4 ml

powder and solvent for solution for injection

glutathione

V03AB32



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AIFA submission date 24th january 2004

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glutathione

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