Description

The present invention relates to polychemotherapeutic compositions comprising at least two anti-tumor agents and reduced glutathione (GSH) as associated preparations to be used simultaneously, separately or sequentially in anti-tumor therapy.

Representative examples of drugs introduced in anti-tumor chemotherapy are: cis-diamine-dichloro-platinum, also referred to as CDDP or cis-platinum, cyclophosphamide, 5-fluorouracyl, doxorubicin (adriamycin), metaxanthrone, methotrexate, etoposide, vincristine and bleomycin; each being characterized by different mechanisms of action and by different schedules of administration.

Few cancer chemotherapeutic agents are effective as single agents; most of them are often used in combination with other anti-tumoral agents so employing a variety of different mechanisms to kill malignant cells.

Polychemotherapeutic antitumoral regimens are is particularly preferred for management of those tumoral forms that are refractory to a single agent (as it often happens in certain cases of solid tumors), with the aim of obtaining the highest possible index of remission of the disease and of preventing the onset of resistance to a single chemotherapeutic agent.

Each cancer chemotherapeutic agent unfortunately induces side-effects and toxicity that are often so serious to prevent the continuation of therapy, thus precluding the final success of therapeutical schemes. Combined use of anti-tumor agents, according to the usual practice of chemotherapy, causes even more the cumulative onset of all side-effects of the single compounds.

For instance, the side-effects pattern becomes more serious when two or more of these compounds are used in combination or together with other anthracycline (e.g. adriamycin) or anthraquinone compounds, that have myocardiotoxicity as the most serious additional side-effect.

An attempt to improve the therapeutic possibilities in the treatment of tumors, is accomplished either by finding out new and more active agents, with a minor toxicity (see for example the new cis-platinum complexes, e.g. compounds known as NSC 311056, NSC 241240 and NSC 256927, widely tested), or in a more immediate way by increasing the therapeutic index of compounds already available by means of treatments to be carried out simultaneously with antineoplastic agents. Up to now, the latter approach has been mainly used in order to correct and limit the side-effects inseparable from the anti-neoplastic therapy itself.

So, for example, in order to limit the dose-dependent nephrotoxic effect induced by cis-platinum in 80-90% of cases, with noticeable tubular damages shown by the increase of urinary levels of N-acetyl-glucosaminidase (NAG) and of alanine-aminopeptidase (AAp), the patients are subjected to a forced-hydration regimen by means of prolonged intravenous infusions with saline, glucose or mannitol solutions.

Said protective treatment, which is anyhow quite uncomfortable for the patient, is necessary, but turns out to be sometimes insufficient, especially in those cases when administration of large quantities of platinum complexes is required.

Moreover, the same protective treatment could be dangerous in case of renal insufficiency and/or in the presence of cardiovascular diseases, as a consequence of the great amounts of the fluids which are necessarily administered.

Thus, for example, prevention of toxic damages, particularly urotoxicity, induced by cytostatic oxazaphosphorinic agents is pursued by concomitant administration of mercapto-alkane-sulphonic acids as disclosed by EP-A-000 2495.

Otherwise, animal experiments seem to suggest that preventive and sequential administration of a natural thiol compound as well as reduced glutathion (γ -glutamyl-cysterinyl-glycine) could be useful for preventing renal- and urotoxicity induced by both the anti-tumor agents: cyclophosphamide and cis-platinum [see for example Tumori 69 , 105 (1983) and Cancer, Chemother., Pharmac. 14 , 188, 1985]. Unfortunately, the extremely high dosages of GSH (from 200 mg/kg up to 4 g/kg in divided doses) used in said experimental studies for achieving some beneficial effects rules out any real utility of this natural thiol in the clinical practice.

Useful doses in men would require the administration of 15-280 g of GSH, adding serious practical problems to those already perceived during the hydration regimen.

Current knowledge (vide infra) looking at the lowering of intracellular GSH level as a therapeutical aim to be pursued in order to favour antineoplastic therapy further discourages this approach.

However, reduced GSH has been recently proposed as an effective and clinically useful protecting agent in men, to reduce side-effects (particularly tubular damage) of platinum complexes in particular "cis-platinum",GB-A-2174905 (Italian Patent Appln. No. 20591 A/85 of 6th May, 1985) and is administered in a dose range from 2,5 to 5g as a total dose by an infusional route.

Said treatment, not changing the hydration regimen, is claimed to limit tubular damage, as shown by NAG and AAP enzymes determination in urine, without significant detrimental effects on anti-tumor activity.

All these known treatments do not allow however the increase of administration dosages of anti-tumoral compounds to the level that should be necessary in particular conditions of natural or induced resistance (for example in most cases of solid tumors, in particular those of lungs and colon).

A great effort has been recently made to find substances which are able to restore the sensitivity of resistant cells to drugs such as doxorubicine, vincristine, cis-platinum and can possibly increase the cytotoxicity.

So, for example, calmodulin, an ubiquitous calcium-binding protein, responsible for many of the intracellular actions of calcium, was recently proposed as a potential target for cancer chemotherapeutic agents, [W.H. Hait, J. of Clin. Oncol. 4 , 994 (1986)]. Some calmodulin antagonists are themselves cytotoxic substances and various trials are running to prove if their inclusion in traditional cytotoxic chemotherapeutic regimens may extend the efficacy of the currently available drugs.

Recent studies have also concentrated on the use of calcium channel blockers in combination with classical cancer chemotherapeutic agents.

On the other hand, the use of buthionine sulphoximine as a specific agent for depletion of GSH from cells has been proposed (Andrews et al. in Cancer Res. 45 , 6250, 1985) to enhance the cytotoxic activity of compounds such as L-phenylalanine mustard, chlorambucyl, CDDP, mechlorethamine, carboplatinum, dichloroethylendiamine-platinum (II), 1,2-diaminocyclohexyl platinum-[II]-malonate.

Surprisingly, and in contradiction to the above mentioned teachings, we have now found that merely a treatment with GSH, which in itself does not have cytotoxic activity, in combination with at least two anti-tumor agents selected from platinum compounds, oxazaphosphorinic compounds, 5-fluoro-uracyl, methotrexate and antracyclines, in polychemotherapy, does not only protect from the onset of side-effects of said drugs, but it is also able to increase the response rate, i.e. remission, allowing an increase of recoveries (long-lasting remissions of 2 years from the end of treatment).

The object of the invention is therefore provided by polychemotherapeutical compositions containing reduced glutathione (GSH) and at least two of said anti-tumoral drugs in form of combined preparations for the simultaneous, separate or sequential use i n anti-tumor therapy.

According to a preferred embodiment, the invention provides a package containing GSH and the anti-tumor drugs in separated vials, so that they can be administered according to the most suitable administration schemes.

The term "platinum compounds" according to the invention includes preferably cis-dichlorodiamine-platinum. Others compounds which may be used comprise, for instance, carboplatinum, dichloro-ethylenediammine-platinum (II), 1,2-diaminocyclohexyl-platinum[II]-malonate or sulphate, diisopropylamino-trans-dihydroxy-cis-dichloro-platinum IV.

The meaning of oxazaphosphorinic compounds comprises the well known cyclophosphamide and iphosphamide .

Finally, anthracycline compounds include preferably doxorubicin (adriamycin). Others compounds usable according to the invention include epirubicin, daunorubicin and carmamycins, mitoxanthrone analogs.

The above compounds are usually used in combination, according to suitable protocols of poly-chemotherapy.

Thus, it is possible to administer a combination of anti-neoplastic agents, e.g. platinum (II) - or platinum (IV) complexes together with cyclophosphamide and methotrexate.

Of course, any other possible combination of anti-neoplastic agents mentioned in this application is also possible and lies within the knowledge of a person skilled in the art.

The administration of GSH proved to be particularly advantageous in combination with the platinum complexes.

For instance, it has been noticed that the administration of cis-platinum in combination with glutathione leads not only to a dramatic decrease in side-effects such as nephro- and neurotoxicity which can be normally observed when cis-platinum alone is administered, but, above all, surprisingly shows that the efficacy in anti-tumor activity expressed as remission rate and disease free survival is increased. Moreover, the administration of higher amounts of cis-platinum should be especially advantageous in those cases in which a higher dosage is required to sufficiently effect the treatment of advanced tumors. It is also surprising that the pre-treatment with glutathione allows, through unknown mechanisms, to use cumulative higher amounts of cis-platinum in each course, achieving thereby an higher efficacy even in advanced stages. This was not possible when cis-platinum alone was administered due to the accompanying high toxicity and severe side-effects in connection therewith.

In fact, the maximum applicable dosage is about 1000 mg/m^2, which means an increase of 600-400

mg/m² in comparison to the maximum dosage of 400-600 mg/m² when cis-platinum was administered without glutathione. In the latter case severe side-effects had to be taken into consideration.

In similar manner as described above the myocardial toxicity evolved by the use of doxorubicin is decreased, when administered in combination with glutathione. A comparable effect is observed (reduced myelo- and bladder-toxicity) when cyclophosphamide or methotrexate is administered.

The most surprising aspect of the present invention is provided by the synergistic effect of GSH and the above cited anti-tumor agents, although part of the above discussed scientific literature teaches that an intracellular GSH depletion is desirable for enhancing the antitumoral activity.

Said synergism is moreover also particularly surprising in view of the fact that GSH, administered alone, is completely devoid of any antitumor activity.

These unpredictable effects, which could be therefore referred to as "synergism", are evident when a selected dosage regimen is used, namely 2.5 to 5 g of glutathione, approximately corresponding to 1500 mg/m² - 3000 mg/m² of GSH (considering the mean body surface to be about 1.4 m² for women and about 1.7 m² for men) whereas each anti-tumor agent is administered at the doses usually known in therapy, or higher doses, as stated above, since the administration of GSH allows a considerable increase of the dose of the anti-tumor drugs, without the onset of toxicity symptoms. This often causes significant improvements in the overall therapeutic results.

Higher doses of GSH proved to be uncomfortable for the administration to patients, with possible decrease of anti-tumor efficacy, whereas lower doses induced only minor improvements in the tolerability of the anti-tumor drug.

Another important advantage of the invention, obviously when platinum compounds are used, is that forced-hydration may be drastically reduced when the patient is pre-treated with GSH.

The doses of the anti-tumoral drugs according to the invention are well known in the art, see for instance Goodman & Gilman, The Pharmacological Basis of Therapeutics VII Ed. Mac Millan Pub. Co., N.Y. 1985, pp. 1240-1306. For instance, as far as platinum complexes are concerned, and with particular reference to cis-dichlorodiamine-platinum, two dosage regimens are widely used:
the first consists in the administration of 90 mg/m² at the day 1 - then 3 weeks of wash-out, followed by further 4 treatments, always every 3 weeks, reaching therefore a total dose of 450 mg/m².

The other regimen consists in administering 40 mg/m² of CDDP daily for 5 days (200 mg/m² total) and said treatment should be continued for at least 5 weeks, up to a total dose of 1 g/m². However, in the therapeutical practice, the treatment is usually interrupted after 2 or 3 cycles (400 mg/m² or 600 mg/m²) because of the onset of serious, even fatal, side-effects.

The contemporaneous administration of 1.5 g/m² or 3 g/m² of GSH produces in both cases beneficial effects, allowing the completion of the regimen, up to the maximum permissible doses.

When cyclophosphamide or iphosphamide is used, from 0.5 g to 4 g of GSH per g of cyclophosphamide are generally sufficient, in order to obtain the effects according to the invention.

In the case of anthracyclines, with particular reference to doxorubicin, the ratio GSH/doxorubicin, is ranging from 20 to 50 mg of GSH per mg of anthracycline.

Since anthracycline is usually administered at doses ranging from 30 to 60 mg/m², the GSH dosage is from 1 to 5 g.

As far as methotrexate is concerned, it should be noted that the clinical dosage may be remarkably variable.

An i.v. dose of 50/250 mg/m² is usually referred to a "low" dosage, an i.v. dose of 1-2 g/m² as an "intermediate" dosage, and 10 g/m² as an "high" dosage. In said conditions, the ratios between GSH and methotrexate are correspondingly variable, for instance from 0.3 to 15 mg of GSH per mg of methotrexate, corresponding to total GSH dosages from 1 to 5 g.

The mean weight ratios for selected anti-tumor agents are hereinbelow summarized:

Anti-tumor agent	mg GSH/mg anti-tumor agent
Cis-dichlorodiamineplatinum	20-100 mg
Cyclophosphamide	0.5-4 mg
Doxorubicin	20-50 mg
Methotrexate	0.3-15 mg

The compositions according to the invention may be prepared using usual methods and excipients, such as described in "Remington's Pharmaceutical Sciences Handbook", Hack Pub. Co., New York, USA.

The administration routes are those commonly used in a eoplastic therapy, namely the intravenous route (either by bolus or infusion) and, in case of methotrexate, also the oral route.

The most common route is however the infusional one, according to dosage regimens already established in medical praxis and which are within the skill of any expert in the art.

The infusion solution is a physiologically acceptable solution, especially a isotonic solution, which can also contain a necessary amount of a salt, e.g., sodium chloride, or glucose and optionally viscosity regulating compounds, such as polyethyleneglycols or polypropyleneglycols.

As far as GSH is concerned, the preferred dilution is 1 g of GSH in 40 ml of a saline physiological or glucose-physiological solution, to be administered from 15 minutes to 2 hours before the administration of the antitumoral drugs.

The oral administration may also be suitable for GSH and for methotrexate. In this case, suited formulations comprise capsules, tablets, granulates and syrups.

The glutathione and the anti-tumor agents may be admixed in a unit dose form. Separate unit doses are however preferred, because of the resulting flexibility of therapeutical schemes.

In the following examples that illustrate but do not limit the invention, the efficacy of this treatment and importance of side-effects (nausea, vomiting, myelodepression, leucopenia, piastrinopenia, nephrotoxicity, azotemia, creatinemia, urinary levels of NAG and AAP enzymes) are evaluated.

EXAMPLE 1

A composition of cis-platinum + cyclophosphamide + GSH was administered to 7 patients suffering from advanced ovarian tumors, not previously treated. The schedule of treatment was the following: cis-platinum 90 mg/m^2 i.v. in 250 ml normal saline over 30 min., cyclophosphamide 600 mg/m^2 i.v. GSH 1.5 g/m^2 in 100 ml of normal saline, 15 min. before cis-platinum. This schedule was repeated every three weeks, for 5 cycles. One patient was dropped out from the evaluation because affected by a different neoplasia (colon carcinoma). The remaining six patients (I stage II, 4 stage III and 1 stage IV) received a standard i.v. pre and post -hydration, which consisted of 2000 ml fluids. Diuretics were not used on a routine basis. The patients received a total of 28 courses with GSH at 1500 g/m^2 dose level.

No symptoms of urotoxicity, nephrotoxicity, myelotoxicity and neurotoxicity were observed; side effects such as nausea and vomiting were very mild in contrast to those observed without GSH supplementation treatment. There was no evidence of severe myelosuppression.

First of all, the results put in evidence the lack of negative interference of GSH on the therapeutic efficacy of cis-platinum. In fact 6/6 patients with advanced disease achieved complete remission (pathologically documented); five are still in remission after more than 24 months of follow-up and, unfortunately, one had relapse after 20 months of disease-free interval. She is still alive with brain

metastasis after 24 months.

In spite of a small number of patients treated, it is to be pointed out that in similar occasions frequency of full remissions two years after end of the treatment is only 5-10%.

EXAMPLE 2

Nine patients with ovarian cancer at high risk of relapse after radical surgery received treatment with a composition of cis-platinum + cyclophosphamide + GSH. All the patients were not previously treated with other antineoplastic agents.

The schedule treatment was the following:

cis-platinum (90 mg/m^2, administered i.v. in 280 ml of normal saline over 30 min.), cyclophosphamide (600 mg/m^2 i.v.) and GSH (3 g/m^2). This schedule was repeated every three weeks.

All the patients (6 stage I, 2 stage II, 1 stage III) received a reduced i.v. hydratation (1000 ml fluids) and GSH (3 g/m^2), in 200 ml of normal saline, given i.v. over 15 min. prior to each cis-platinum administration.

Diuretics were not used on a routine basis.

No nephrotoxic and neurotoxic manifestations were observed, there is no evidence of severe myelosuppression.

The side effects were very mild as after previous protocol of administration, whereas the reduced hydratation, increased the patient's compliance avoiding any possible side effects due to the amount of fluids otherwise administered.

The patients were submitted to 44 courses up to now; five patients have no evidence of disease after the end of five courses and four are still under treatment.

The results strongly support that GSH does not reduce the antitumor activity of cis-platinum, the use of GSH represents an alternative safer method for delivering high doses of platinum-complexes and for surprisingly increasing remission rate.

EXAMPLE 3

6 patients with advanced head and neck cancer, pre-treated with radiotherapy and surgery, and in a relapse phase of the disease, were treated with a combination of cis-platinum (100 mg/m^2 i.v. in 100 ml normal saline) + 5-fluorouracyl (1 g/m^2 i.v. in 500 ml normal saline) every two weeks for 2-4 treatment courses. GSH was contemporaneously administered (i.v. in 100 ml normal saline) up to a total dose of 5 g/m^2, at the end of treatment.

All patients achieved an important objective response occurring a few days after treatment. In all patients a reduction and/or disappearance of tumoral lesions was noticed with surprising important relief in the overall conditions, one year after treatment. No side-effects were noticed.

Claims

1. Use of Glutathione (GSH) for the preparation of a pharmaceutical composition for the polychemotherapeutical treatment of tumor diseases consisting of a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usual excipients, wherein the total amount of GSH is from 2,5 to 5,0 g and the GSH and the anti-tumor agents are each in separate or unit dose forms.

2. Use of GSH according to claim 1, wherein the platinum complex is cis-dichlorodiamine-platinum.

3. Use of GSH according to claim 1 or 2, wherein the other antitumor agents are selected from cyclophosphamide, methotrexate, doxorubicin (adriamycin) and 5-fluorouracyl.

4. Pharmaceutical kit consisting of GSH and a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usual excipients, wherein the total amount of GSH is from 2,5 to 5,0 g and the GSH and the anti-tumor agents are each in a separate dose form.

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Claims

1. Use of Glutathione (GSH) for the preparation of a pharmaceutical composition for the polychemotherapeutical treatment of tumor diseases consisting of a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usual excipients, wherein the total amount of GSH is from 2,5 to 5,0 g and the GSH and the anti-tumor agents are each in separate or unit dose forms.

2. Use of GSH according to claim 1, wherein the platinum complex is cis-dichlorodiamine-platinum.

3. Use of GSH according to claim 1 or 2, wherein the other antitumor agents are selected from cyclophosphamide, methotrexate, doxorubicin (adriamycin) and 5-fluorouracyl.

4. Pharmaceutical kit consisting of GSH and a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usual excipients, wherein the total amount of GSH is from 2,5 to 5,0 g and the GSH and the anti-tumor agents are each in a separate dose form.

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Claims for the following Contracting States: AT, ES, GR

1. Process for the preparation of a pharmaceutical composition for the polychemotherapeutical treatment of tumor diseases consisting of a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usual excipients, wherein the total amount of Glutathione CGSH)is from 2,5 to 5,0 g and the GSH and the anti-tumor agents are each in separate or unit dose forms.

2. Process according to claim 1, wherein the platinum complex is cis-dichlorodiamine-platinum.

3. Process according to claim 1 or 2, wherein the other anti-tumor agents are selected from cyclophosphamide, methotrexate, doxorubicin (adriamycin) and 5-fluorouracyl.

4. Process for the preparation of a pharmaceutical kit consisting of GSH and a platinum complex and other anti-tumor agents selected from oxazaphosphorines, anthracyclines, 5-fluorouracyl and methotrexate and optionally usually excipients said GSH being present in a total amount of 2,5 - 5,0 g wherein the GSH and the anti-tumor agents are provided each in a separate dose form.

Revendications

1. Utilisation du glutathion Pour la préparation d'une composition pharmaceutique pour le traitement polychimiothérapique d'affections tumorales, comprenant un complexe du platine et d'autres agents antitumoraux choisis parmi les oxazaphosphorines, les anthracyclines, le 5-fluorouracyle et le méthotrexate, et éventuellement des excipients usuels, dans lequel la quantité totale de GSH est de 2,5 à 5,0 g et le GSH et les agents antitumoraux sont chacun sous des formes d'administration séparées ou unitaires,

2. Utilisation du GSH selon la revendication 1, dans laquelle le complexe du platine est le cis-dichlorodiamine-platine.

3. Utilisation du GSH selon la revendication 1 ou 2, dans laquelle les autres agents antitumoraux sont choisis parmi le cyclophosphamide, le méthotrexate, la doxorubicine (adriamycine) et le 5-fluorouracyle.

4. Kit pharmaceutique, constitué de GSH et d'un complexe du platine et d'autres agents antitumoraux choisis parmi les oxazaphosphorines, les anthracyclines, le 5-fluorouracyle et le méthotrexate, et éventuellement des excipients usuels, dans lequel la quantité totale de GSH est de 2,5-5,0 g, et le GSH et les agents antitumoraux sont fournis chacun sous une forme d'administration séparée.

REVENDICATIONS pour les Etats contractants suivants: AT, ES, GR

1. Procédé pour la préparation d'une composition pharmaceutique pour le traitement polychimiothérapique d'affections tumorales, comprenant un complexe du platine et d'autres agents antitumoraux choisis parmi les oxazaphosphorines, les anthracyclines, le 5-fluorouracyle et le méthotrexate, et éventuellement des excipients usuels, dans lequel la quantité totale de glutathion (GSH) est de 2,5 à 5,0 g et le GSH et les agents antitumoraux sont chacun sous des formes d'administration séparées ou unitaires.

2. Procédé selon la revendication 1, dans lequel le complexe du platine est le cis-dichlorodiaimine-platine.

3. Procédé selon la revendication 1 ou 2, dans lequel les autres agents antitumoraux sont choisis parmi le cyclophosphamide, le méthotrexate, la doxorubicine (adriamycine) et le 5-fluorouracyle.

4. Procédé pour la préparation d'un kit pharmaceutique, constitué de GSH et d'un complexe du platine et d'autres agents antitumoraux choisis parmi les oxazaphosphorines, les anthracyclines, le 5-fluorouracyle et le méthotrexate, et éventuellement des excipients usuels, ledit GSH et les agents antitumoraux étant présents en une quantité totale de 2,5-5,0 g, dans lequel le GSH et les agents antitumoraux sont fournis chacun sous une forme d'administration séparée.

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Ansprüche

1. Verwendung von Glutathion (GSH) für die Herstellung eines pharmazeutischen Präparates zur polychemotherapeutischen Behandlung von Tumorerkrankungen, das aus einem Platinkomplex und anderen Antitumormitteln, die aus Oxazaphosphorien, Anthracyclinen, 5-Fluoruracil und Methotrexat ausgewählt sind, und gegebenenfalls üblichen Zusatzstoffen besteht, wobei die Gesamtmenge an GSH 2,5 bis 5,0 g beträgt und das GSH und die Antitumormittel jeweils in getrennten oder in einer einheitlichen Darreichungsform vorliegen.

2. Verwendung von GSH nach Anspruch 1, worin der Platinkomplex cis-Dichlordiammin-Platin ist.

3. Verwendung von GSH nach Anspruch 1 oder 2, worin die anderen Antitumormittel aus Cyclophosphamid, Methotrexat, Doxorubicin (Adriamycin) und 5-Fluoruracil gewählt sind.

4. Pharmazeutische Verpackungseinheit, die aus GSH und einem Platinkomplex und anderen Antitumormitteln, die aus Oxazaphosphorinen, Anthracyclinen, 5-Fluoruracil und Methotrexat gewählt sind, und gegebenenfalls üblichen Zusatzstoffen besteht, wobei die Gesamtmenge an GSH 2,5 bis 5,0 g beträgt und das GSH und die Antitumormittel jeweils in einer getrennten Darreichungsform vorliegen.

Patentansprüche für folgende Vertragsstaaten: AT, ES, GR

1. Verfahren zur Herstellung eines pharmazeutischen Präparates zur polychemoterapeutischen Behandlung von Tumorerkrankungen, das aus einem Platinkomplex und anderen Antitumormitteln, die aus Oxazaphosphorinen, Anthracyclinen, 5-Fluoruracil und Methotrexat ausgewählt sind, und gegebenenfalls üblichen Zusatzstoffen besteht, wobei die Gesamtmenge an Gluthathion (GSH) 2,5 bis 5,0 g beträgt und das GSH und die Antitumormittel jeweils in getrennten oder einheitlichen Darreichungsformen vorliegen.

2. Verfahren nach Anspruch 1, worin der Platinkomplex cis-Dichlordiammin-Platin ist.

3. Verfahren nach Anspruch 1 oder 2, worin die anderen Antiturmormittel aus Cyclophosphamid, Methotrexat, Doxorubicin (Adriamycin) und 5-Fluoruracil gewählt sind.

4. Verfahren zur Herstellung einer pharmazeutischen Verpackungseinheit, die aus GSH und einem Platinkomplex und anderen Antitumormitteln, die aus Oxazaphosphorinen, Anthracyclinen, 5-Fluoruracil und Methotrexat gewählt sind, und gegebenenfalls üblichen Zusatzstoffen besteht, wobei das GSH in einer Gesamtmenge von 2,5 bis 5,0 g vorhanden ist und das GSH und die Antitumormittel jeweils in einer getrennten Darreichungsform vorgesehen sind.

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