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(54) Benevnelse **COMPOSITION COMPRISING A COMBINATION OF DHA AND EPA FOR PARENTERAL ADMINISTRATION PRIOR TO COMMENCEMENT OF CHEMOTHERAPY**

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COMPOSITION COMPRISING A COMBINATION OF DHA AND EPA FOR PARENTERAL ADMINISTRATION PRIOR TO COMMENCEMENT OF CHEMOTHERAPY

The intravenous application of fish oil/DHA + EPA prior to or with commencement of chemotherapy

Field of the Invention

The present invention relates to the use of a composition comprising omega-3 fatty acids for administration to cancer patients prior to commencement of a cycle of chemotherapy or radiotherapy. Through the administration of the composition, the efficacy of the therapy is improved. Side effects of the therapy are prevented or moderated through the administration of the therapy.

Background of the Invention

Throughout the world, cancer diseases are one of the commonest causes of death. The commonest cancer diseases in women are mammary carcinoma, lung carcinoma and colorectal carcinoma. Men particularly commonly contract prostate carcinoma, lung carcinoma and colorectal carcinoma (Jemal et al. 2009; CA Cancer J Clin; 59(4): 225-49). Common to all cancer diseases is that changes in the cell lead to its uncontrolled growth.

Depending on the nature and location and depending on the disease stage, treatment of the cancer disease is effected by surgical removal of the tumour, chemotherapy, radiotherapy, immunotherapy or further, so-called targeted forms of therapy, which for example include treatment with monoclonal antibodies. In principle, chemotherapy and radiotherapy can be used as the only therapy. Often, however, depending on the patient's disease stage, several forms of therapy are combined. For example, a tumour is often first removed surgically, and chemotherapy used thereafter in order to kill any cancer cells that have remained in the body. Radiotherapy can for example be used in order firstly to achieve shrinkage of the tumour, which facilitates the subsequent surgical removal of the tumour. A combination of chemotherapy and radiotherapy

("radiochemotherapy") is used inter alia in the treatment of tumours of the rectum, the uterine cervix, the lung, the thorax and the oesophagus and in head-neck tumours.

In spite of improved therapeutic possibilities for patients with cancer diseases the disease is in many cases not causally treatable. Here the therapy can only under some circumstances slow the progression of the disease (Jemal et al. 2009; CA Cancer J Clin; 59(4): 225-49).

The chemotherapeutic agents used for the treatment of cancer diseases and also the commonly used radiotherapy cause severe side effects in the patients (Ladewski et al. 2003; J Clin Oncol. 21(20):3859-66). This is to be explained in that the action of chemotherapeutic agents and radiotherapy is not confined to the cancer cells. Damage to healthy cells occurs. Especially affected are cells which exhibit strong mitotic activity, such as for example the cells of the mucous membranes. Stomatitis, mucositis, vomiting and diarrhoea are for example observed. Other side effects affect the haematopoietic system, and nerve cells can also be affected.

The severe side effects which are usually associated with cancer therapy stress the patients and in the end are also a crucial factor in determining to what extent or at what dosage chemo- or radiotherapy can be used.

WO98/09621 describes the cytotoxic effects of various fatty acids, inter alia those of EPA and DHA, and their moderating action as regards the chemotherapy-related side effects of a cancer treatment. However, WO98/09621 makes no specific statements as to the actual dosage scheme nor in particular as to the time at which the fatty acids should be administered.

The supplementation of cancer patients with EPA in the period from one week prior to the operation to 2 weeks after the operation in addition to administration of a postoperative chemotherapy possibly has positive effects on the overall survival of the patients (Nutrition Volume 17, Number 6, 2001, S. 478-479). However, such a dosage

scheme must be planned long-term and consequently does not justify short-term and/or spontaneous intervention.

There is therefore still a need for compositions and methods for preventing or weakening the occurrence of side effects in cancer therapies. Thereby, the tolerance, efficacy and acceptance of the therapy by the patients could be improved. Further, there is a need for compositions and methods for increasing the efficacy of chemo- or radiotherapy. Increased efficacy enables the reduction of the dosages to be used for the therapy and thereby also a decrease in the side effects associated with the therapy.

Summary Description of the Invention

The invention relates to a composition comprising omega-3 fatty acids. The composition can be used in improving the efficacy of chemotherapy or radiotherapy and/or in the prevention or reduction of side effects caused by chemotherapy or radiotherapy in a patient suffering from cancer, wherein the composition should be administered to the patient prior to commencement of a cycle of chemotherapy or radiotherapy.

Figures

Figure 1: Application scheme for administration of a composition comprising EPA and DHA (Omegaven®) prior to commencement of a cycle of chemotherapy. The figure shows by way of example the consecutive intravenous application of Omegaven® two days ("day 1") and one day ("day 2") prior to commencement of a cycle ("day 3") of a 5-FU-based adjuvant chemotherapy in a patient with colorectal carcinoma. The chemotherapy scheme used is the so-called FOLFOX scheme. FOLFOX is a combination therapy consisting of the drugs folinic acid, fluorouracil and oxaliplatin. FOLFOX is the most widespread therapeutic scheme for the treatment of colon carcinoma. The dosage information for the chemotherapy drugs is given as mg/m^2 of the patient's body area. The administration of Omegaven® is effected at a dosage of 2 mL/kg patient's bodyweight and day. The representation of the

composition and drugs administered are schematic and the width of the bars does not correspond to the duration of administration.

Figure 2: Application scheme for administration of a composition comprising EPA and DHA (Omegaven®) prior to commencement of a cycle of chemotherapy, wherein administration is also effected 3 hours prior to commencement of the cycle. The figure shows by way of example the consecutive intravenous application of Omegaven® two days ("day 1"), one day ("day 2") and on the day of commencement ("day 3") of a cycle of a 5-FU-based adjuvant chemotherapy according to the FOLFOX scheme in a patient with colorectal carcinoma. The administration on the day of commencement of the chemotherapy cycle is effected 3 hours ("-3 h") prior to commencement of the cycle, and is ended at the latest one hour ("-1 h") prior to commencement of the cycle. The dosage information for the chemotherapy drugs is given as mg/m^2 of the patient's body area. The administration of Omegaven® is effected at a dosage of 2 mL/kg patient's bodyweight and day. The representation of the composition and drugs administered are schematic and the width of the bars does not correspond to the duration of administration.

Figure 3: Application scheme for administration of a composition comprising EPA and DHA (Omegaven®) prior to commencement of each cycle of a chemotherapy comprising 12 cycles. The figure shows by way of example the consecutive intravenous application of Omegaven® two days and one day prior to each cycle of a 5-FU based adjuvant chemotherapy according to the FOLFOX scheme comprising 12 cycles in a patient with colorectal carcinoma. The administration is effected each time prior to commencement of a cycle. One cycle of the chemotherapy comprises two days. The cycle is followed by a multiday treatment pause, in which the patient receives no chemotherapeutic agents, and which extends until the commencement of the next cycle of chemotherapy. This is followed by the second cycle of chemotherapy. Omegaven® is administered prior to the second cycle, namely during the treatment pause. The administration scheme for Omegaven® is implemented identically for the following cycles 3 to 11 (not shown). Thus Omegaven® is administered two days and one day prior to commencement of the respective

cycle of chemotherapy. In principle, however, variations in the administration scheme are also possible, provided that the administration is effected prior to commencement of the cycle, and provided that the administration does not fall into the cycle preceding the respective cycle. The administration prior to the twelfth (last) cycle of the chemotherapy is effected as described above for cycles 1 to 11. The representation of the composition and drugs administered are schematic and the width of the bars does not correspond to the duration of administration.

Figure 4: Influence of DHA and EPA on the survival of HT-29 cells after irradiation. The figure shows the survival of HT-29 cells after a two-day pretreatment with 20 µM to 100 µM DHA (A) or EPA (B) followed by irradiation with 0 Gy (white bars), 2 Gy (light grey bars), 4 Gy (mid-grey bars) or 6 Gy (black bars). The values are stated as mean values (%) ± standard deviation relative to the untreated controls (6 per group). * $P < 0.05$ in comparison with 0 Gy; § $P < 0.05$ in comparison with untreated control.

Detailed Description of the Invention

The invention is defined by the appended claims.

Definitions:

The term administration comprises enteral and parenteral administration.

Enteral administration designates introduction via the intestine, for example by oral ingestion, or by transnasal, gastric or jejunal probes.

Parenteral administration in the sense of the invention here present is understood to mean administration bypassing the intestine. Comprised thereby are thus for example intravenous injection or infusion and intraarterial injection or infusion. Administration into an arterial blood vessel is understood to be **intraarterial**, and administration into a venous blood vessel as **intravenous**. Injection comprises administration via syringe. As a rule, this is effected as a bolus. However, continuous injection by means of syringe pumps is also possible. Infusion designates the continuous administration of

the composition into a blood vessel, which can for example be effected via a peripheral or central venous catheter. Also comprised is **transdermal** administration (administration via the skin).

Chemotherapy is understood to mean the drug therapy of cancer diseases. Chemotherapy can comprise treatment with one or more drugs, so-called **chemotherapeutic agents**, for the therapy of cancer diseases. A combination of drugs can be used, which are administrated simultaneously, or at different times. Chemotherapeutic agents which are used for the drug therapy of cancer diseases are in some cases also used for the treatment of other diseases, such as for example severe autoimmune diseases.

FOLFOX is a chemotherapy scheme used for chemotherapy of colorectal carcinoma, comprising the drugs oxaliplatin, folinic acid (Leucovorin) and fluorouracil (5-FU).

FOLFIRI is also a chemotherapy scheme used for chemotherapy of colorectal carcinomas, comprising the drugs folinic acid (Leucovorin), fluorouracil (5-FU) and irinotecan.

Radiotherapy comprises the use of ionizing radiation, for example gamma radiation, X-rays and electrons. Also comprised is the use of neutrons, protons and heavy ions for the treatment of cancer patients. Radiotherapy can for example be effected in the form of teletherapy or brachytherapy. In the sense of the invention here present, the expression “administration of an irradiation” or “administration of the irradiation" can be used equivalently with the expression “irradiation”.

A **cycle** in the sense of the invention here present is understood to mean a period in which an irradiation, a chemotherapeutic agent, several chemotherapeutic agents or a combination thereof are administered to a patient. In case of single administration of the irradiation, the chemotherapeutic agent, several chemotherapeutic agents or a combination thereof, the cycle comprises the period from commencement of the single administration until the end of the single administration.

If an irradiation, a chemotherapeutic agent, several chemotherapeutic agents or a combination are administered on successive days, then the cycle comprises the period from commencement of the first administration until the end of the last administration. The administration of the irradiation, the chemotherapeutic agent, the chemotherapeutic agents or a combination thereof can be effected simultaneously or at different times and can be repeated singly or in combination. If the patient on a day following administration of an irradiation, a chemotherapeutic agent, chemotherapeutic agents or a combination thereof receives neither irradiation nor a chemotherapeutic agent nor several chemotherapeutic agents, the cycle is completed with the end of the last administration.

The cycle is followed by a treatment pause. This is characterized in that no irradiation and no chemotherapy are administered to the patient during the treatment pause.

One or more cycles can follow a treatment pause. A chemotherapy or radiotherapy can thus comprise one or more cycles.

The **commencement of the first cycle** of chemotherapy or radiotherapy can be the time from which a patient for the first time receives a certain chemotherapy or a certain radiotherapy, that is the time from which an irradiation, a chemotherapeutic agent, several chemotherapeutic agents or a combination are for the first time administered to the patient. The **commencement of a cycle** is the time at which the administration of an irradiation, a chemotherapeutic agent, several chemotherapeutic agents or a combination thereof commences. If more than one element selected from the group of irradiation, a chemotherapeutic agent, and several chemotherapeutic agents are administered, then the cycle commences with the commencement of the administration of the element which is administered as the first, and ends with the end of the administration of the element which is administered as the last.

Solid tumours according to the invention here present comprises tumours which are not derived from the haematopoietic system. Solid tumours are solid, initially localized

tumours. The term also comprises colonizations of the tumour into other organs, so-called metastases. Solid tumours can be benign or malignant. If a malignant solid tumour occurs in a patient, then the patient is suffering from cancer. All types of solid tumours are included. Preferred solid tumours are colorectal carcinoma, mammary carcinoma, pancreatic carcinoma, liver carcinoma, lung carcinoma, and gastric carcinoma. Quite especially preferred is colorectal carcinoma.

The term **non-solid tumours** according to the invention here present comprises cancer types of the haematopoietic system. The term also comprises colonizations into other organs, so-called metastases. The non-solid tumours include the leukaemias, comprising acute myeloid leukaemia (AML, also described as acute non-lymphatic leukaemia (ANLL)), chronic myeloid leukaemia (CML), acute lymphatic leukaemia (ALL), chronic lymphatic leukaemia (CLL) and lymphoma, comprising Hodgkin lymphoma and non-Hodgkin lymphoma.

The term **colorectal carcinoma** comprises carcinomas of the colon and/or the rectum. Colonizations of colorectal carcinoma into other organs, so-called metastases, are also included.

Improvement of efficacy in the sense of the invention here present is understood to mean an increase in the efficacy of a chemotherapy or radiotherapy. With improved efficacy, the chemotherapy or radiotherapy exerts a stronger action on the tumour at the same dosage. This can lead to parameters such as tumour growth, tumour volume, or tumour cell metastasis, or a combination thereof being favourably influenced. An improvement in the efficacy of a chemotherapy or radiotherapy can for example lead to a more marked decrease in the tumour volume. Likewise, an improvement in the efficacy can lead to the tumour volume remaining constant over a longer period, or the tumour growing less rapidly or less strongly than would be the case without the improvement in the efficacy. An increase in the efficacy of a chemotherapy or radiotherapy can have the result that the dosage of the therapy can be selected lower, and the same action on the tumour that the higher dosage has on the tumour without an

improvement in its efficacy can nonetheless be achieved. An increased efficacy can be caused by increased chemosensitivity of the cells.

In medicine, the term **chemosensitivity** describes the sensitivity of cancer cells to growth-inhibiting cytostatic agents. The chemosensitivity of cancer cells is often decisive for the success of the chemotherapy.

In the sense of the invention here present, **prevention of side effects** is understood to mean prevention of the occurrence of one or more side effects typically associated with a treatment. **Reduction of side effects** is understood to mean moderation of the side effects, that is less strongly marked occurrence or chronologically shortened occurrence of the side effect. The side effects which can be associated with a treatment, and their manifestations, are well known to those skilled in the art.

Side effects are effects which occur in addition to the intended intrinsic action of a drug or form of treatment. Side effects are also described as undesired drug effects.

The side effects of chemotherapy for the treatment of cancer patients include inter alia: gastrointestinal side effects (such as for example dryness of the mouth, inflammation of the mouth, inflammatory changes in the mucous membrane (mucositis) in the gastrointestinal tract, diarrhoea), haematological side effects (such as for example anaemia, thrombopaenia, neutropaenia, leukopaenia, myelosuppression, disturbance of the endogenous immune defence, disturbance of blood clotting), reduction in liver weight, neurotoxic side effects (for example damage to nerves, disturbance of touch sensitivity or sensitivity), side effects affecting the heart such as for example disorders of the heart muscle (cardiomyopathy), inflammatory side effects, weight loss, limited function of the immune system, hair loss, fatigue, nausea, vomiting, or a combination thereof.

The side effects observed with radiotherapy include inter alia: fatigue, anorexia, depression, headaches, nausea, vomiting, diarrhoea, damage to the mucous membrane

of mouth and pharynx, damage to the mucous membrane of the digestive tract, damage to the bladder.

Omega-3 fatty acids are multiply unsaturated fatty acids wherein the last double bond of the fatty acid is present in the omega-3 position, that is in the third last C-C bond viewed from the carboxyl end. The **omega-3 fatty acids** contained in the composition according to the invention can be of plant or animal origin, for example the fatty acids can be obtained from algae or from fish. **Long chain** and **very long-chain** omega-3 fatty acids are preferred. **Omega-3 fatty acids** which are selected from the group consisting of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or a combination thereof, are especially preferred.

Long chain omega-3 fatty acids have a chain length of 12-17 carbon atoms. **Very long chain omega-3 fatty acids** (VLCFA) have a chain length of 18-26 carbon atoms. Examples of VLCFAs are linolenic acid, eicosapentaenoic acid and docosahexaenoic acid.

Eicosapentaenoic acid (EPA) or (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoic acid is a multiply unsaturated fatty acid from the class of the omega-3 fatty acids with the molecular formula $C_{20}H_{30}O_2$.

Docosahexaenoic acid (DHA) or (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10.13,16,19-hexaenoic acid is a multiply unsaturated fatty acid from the class of the omega-3 fatty acids with the molecular formula $C_{22}H_{32}O_2$.

Fish oil is understood to mean oil obtained from fish, which contains omega-3 fatty acids. The fish oil can be obtained from sea fish, for example from pelagic fish. Fish oil which is suitable for parenteral administration in man is described as **highly purified fish oil**.

Medium chain triglycerides (medium chain triglycerides, MCT) are triglycerides which contain fatty acid residues of medium length (a length of 6 to 12 C atoms).

Examples of MCT are caproic acid (C6), caprylic acid (C8), capric acid (C10), and lauric acid (C12), or a combination thereof.

Iron in the sense of the invention here present is understood to mean an iron salt suitable for parenteral application. Further, high molecular weight iron compounds, consisting of a polymeric iron(III) oxide-hydroxide core bonded with a carbohydrate shell are also included. Examples are iron citrate, iron dextran, iron sulphate, iron carboxymaltose, iron(II) chloride, iron hydrogen aspartate, iron(II) iodide, iron oxide, iron(III) phosphate, iron(III) sodium gluconate complex, iron -sucrose complex and iron saccharate complex.

A **consecutive administration** is understood to mean administration an two or more successive days. The consecutive administration can for example be effected on 2, 3, or 4 successive days. Also, 24 hours, but also more or les than 24 hours can lie between two successive administrations. Between two successive administrations, 0 to 48 hours can lie, for example 5 to 42 hours, 10 to 38 hours or 12 to 36 hours. For example, the administration on one day can be effected in the morning, but on the following day at midday or in the evening. It is preferable that 20 to 28 hours, particularly preferably 22 to 26, most preferably 24 hours, lie between two successive administrations. Likewise for example the administration on one day can be effected in the evening, and on the following day in the morning or at midday. Consecutive administration on several successive days does not exclude a multiple administration on the same day. The composition can be administered, once, twice, three times, four times or five times daily.

The present invention is based on the recognition that a composition comprising omega-3 fatty acids can be used for improving the efficacy of chemotherapy or radiotherapy in a patient suffering from cancer. Likewise, the composition can be used for the prevention or reduction of side effects caused by chemotherapy or radiotherapy in a patient suffering from cancer.

The composition comprises at least the omega-3 fatty acids EPA and DHA. The composition can contain further omega-3 fatty acids. Also preferred is a composition comprising long chain or very long chain omega-3 fatty acids. The composition can comprise one or more different **omega-3 fatty acids**. If "omega-3 fatty acids" are mentioned in the plural, one or more omega-3 fatty acids can be comprised, provided that nothing else is specified. If "omega-3 fatty acids" are mentioned in the singular, one or more omega-3 fatty acids can be comprised, provided that nothing else is specified.

The composition can comprise further preferred additives, such as MCTs, iron, or a combination thereof.

The composition can be an emulsion.

The composition is administered parenterally and most preferably intravenously.

The inventors have surprisingly discovered that the efficacy of chemotherapy or radiotherapy is improved if a composition comprising omega-3 fatty acids such as EPA and DHA is administered prior to commencement of a cycle of the therapy. An additional administration during the cycle of the therapy or after completion of the cycle is also possible. The efficacy of chemotherapy or radiotherapy is particularly improved when the composition is administered parenterally. The improvement in efficacy is manifested on cancer cells.

Likewise the inventors have discovered that an administration of the composition prior to commencement of a cycle of the therapy surprisingly also leads to the prevention or reduction of side effects caused by chemotherapy or radiotherapy. A particularly effective prevention or reduction of side effects caused by chemotherapy or radiotherapy takes place with parenteral administration of the composition according to the invention.

The precise mechanism underlying the invention is not known. However, it is probable that through the administration, particularly through the parenteral, for example intravenous, administration of omega-3 fatty acids prior to commencement of a cycle of chemotherapy or radiotherapy, these can be better incorporated into the cell membranes. Then at the commencement of the cycle, omega-3 fatty acids, preferably of EPA and/or DHA, are already present in the cell membrane of healthy cells, where they can counteract the toxicity of the chemotherapeutic agents or the irradiation and thus prevent or reduce their side effects. A weakening of the effect of the chemotherapeutic agents or radiotherapy on the tumour cell is not observed. The protective action of the composition is manifested on the healthy cells.

The inventors have discovered that through the administration of the composition prior to commencement of a cycle of chemotherapy or radiotherapy omega-3 fatty acids such as EPA and/or DHA from the composition are advantageously already available in the body and incorporation into cell membranes has already taken place.

Through the parenteral administration, a high dosage of omega-3 fatty acids such as EPA and/or DHA can advantageously be administered. Through the intravenous administration, the omega-3 fatty acids are rapidly available for incorporation into the cell membrane, and no losses during intestinal absorption take place. The composition according to the invention therefore manifests its efficacy with regard to the prevention or moderation of side effects and the improvement of the efficacy of chemotherapy or radiotherapy particularly rapidly, and also even with small quantities. According to the invention, the composition is first administered 48 hours to 24 hours prior to commencement of a cycle of chemotherapy or radiotherapy. Even if for example the composition is first administered three hours prior to commencement of a cycle, the full efficacy of the composition is ensured through its rapid and direct provision. No tedious supplementation over several weeks is necessary. Nonetheless, consecutive administration on two or more successive days can intensify the incorporation of omega-3 fatty acids, such as DHA and EPA, into the cell membranes. In addition to the administration prior to commencement of a cycle, the composition can also be administered during and/or after a cycle.

Advantageously, omega-3 fatty acids, such as EPA and DHA, with administration of the composition according to the invention are already present prior to commencement of a cycle of chemotherapy or radiotherapy, in contrast to compositions known from the prior art, which have to be administered with the commencement or after commencement of chemotherapy or radiotherapy.

The invention relates to a composition which contains omega-3 fatty acids, such as EPA and/or DHA, and is utilized for use in improving the efficacy of chemotherapy or radiotherapy and/or in the prevention or reduction of side effects caused by chemotherapy or radiotherapy in a patient suffering from cancer.

The composition according to the invention is administered to the patient prior to commencement of a cycle of chemotherapy or radiotherapy.

The composition can in addition to the administration prior to commencement of a cycle also take place during the cycle or after the cycle.

The administration can be effected continuously or intermittently.

The administration can effected parenterally. The parenteral administration is preferably effected intravenously. The intravenous administration can be effected as a continuous infusion or as bolus administration.

The composition can be administered such that an intravenous administration amounts to or does not exceed 0.05 mL to 5.0 mL per kg bodyweight and hour. The intravenous administration can for example amount to or not exceed 0.1 mL to 5.0 mL, 0.5 mL to 5.0 mL, 1.0 mL to 5.0 mL, 1.5 mL to 5.0 mL, 2.0 mL to 5.0 mL, 2.5 mL to 5.0 mL, 3.0 mL to 5.0 mL, 3.5 mL to 5.0 mL, 4.0 mL to 5.0 mL or 4.5 mL to 5.0 mL per kg bodyweight and hour. The intravenous administration can amount to or not exceed 5.0 mL to 0.05 mL, 4.5 mL to 0.05 mL, 4.0 mL to 0.05 mL, 3.5 mL to 0.05 mL, 3.0 mL to

0.05 mL, 2.5 mL to 0.05 mL, 2.0 mL to 0.05 mL, 1.5 mL to 0.05 mL, 1.0 mL to 0.05 mL or 0.5 mL to 0.05 mL per kg bodyweight and hour.

Preferably the intravenous administration is effected such that the administration amounts to or does not exceed 0.5 mL to 3.5 mL per kg bodyweight and hour, more preferably 1.0 mL to 3.0 mL, 1.5 mL to 2.5 mL, most preferably 2.0 mL per kg bodyweight and hour. Also preferred is an intravenous administration which amounts to or does not exceed 0.3 to 0.5 mL per kg bodyweight and hour.

The composition according to the invention can be administered to the patient prior to commencement of the first cycle of chemotherapy or radiotherapy. In a preferred embodiment, the composition according to the invention is administered prior to several cycles, in each case prior to commencement of a cycle of chemotherapy or radiotherapy. It is particularly preferable to administer the composition prior to each of the cycles.

Use of the composition according to the invention for improving the efficacy of chemotherapy or radiotherapy and/or for the prevention or reduction of side effects caused by chemotherapy or radiotherapy is in principle not restricted to certain side effects.

The composition according to the invention is used for improving the efficacy of chemotherapy or radiotherapy and/or prevention or reduction of side effects caused by chemotherapy or radiotherapy, wherein the side effects are preferably selected from the group consisting of gastrointestinal side effects, haematological side effects, reduction in liver weight, neurotoxic side effects, side effects affecting the heart, inflammatory side effects, weight loss, limited function of the immune system, reduction of inflammation or a combination thereof.

Quite especially preferably, the composition according to the invention is used for the prevention or reduction of side effects which occur during chemotherapy or radiotherapy of a colorectal carcinoma.

The composition according to the invention for use in improving the efficacy of chemotherapy or radiotherapy and/or in the prevention or reduction of side effects caused by chemotherapy or radiotherapy in a patient suffering from cancer is in principle not restricted to certain cancer diseases.

The composition can be administered in case of a solid or non-solid tumour disease.

Preferred solid tumours are selected from the group consisting of colorectal carcinoma, mammary carcinoma, pancreatic carcinoma, liver carcinoma, lung carcinoma, and gastric carcinoma. Quite especially preferably the composition is for use in a patient suffering from colorectal carcinoma.

The composition according to the invention can be administered with any form of chemotherapy.

In the chemotherapy, a chemotherapeutic agent can be used which is selected from the group consisting of 5-fluorouracil, gemcitabine, doxorubicin, paclitaxel, mitomycin, cyclophosphamide, epirubicin, arabinosylcytosine, tamoxifen, irinotecan, oxaliplatin, folinic acid, cisplatin, taxane, vinca alkaloids, epipodophyllotoxins, synthetic alkaloids, cytarabine, nitrosurea, dacarbazine, fludarabine, ifosfamide, mitomycin C, tamoxifen or a combination thereof. The chemotherapy can also comprise other and/or further chemotherapeutic agents than those mentioned above.

In particular, the composition can also be used when the patient together with the chemotherapy or radiotherapy is also receiving further drugs and/or enteral or parenteral alimentation.

Preferably the composition according to the invention for use in improving the efficacy of chemotherapy or radiotherapy and/or in the prevention or reduction of side effects caused by chemotherapy or radiotherapy is administered during chemotherapy

comprising 5-fluorouracil (5-FU), preferably wherein the chemotherapy is FOLFOX or FOLFIRI.

The radiotherapy can be selected from the group consisting of teletherapy and brachytherapy.

The composition according to the invention can also be used when the patient is receiving chemotherapy and radiotherapy. If the cycle of chemotherapy and radiotherapy does not commence at the same time, the composition according to the invention should preferably be administered prior to that one of the two cycles which commences at the earlier time.

The composition according to the invention can comprise 0.5 g/100 mL to 10.0 g/100 mL EPA. The composition can comprise 1 g/100 mL to 10.0 g/100 mL EPA, 1.5 g/100 mL to 10.0 g/100 mL EPA, 2 g/100 mL to 10.0 g/100 mL EPA, 2.5 g/100 mL to 10.0 g/100 mL EPA, 3 g/100 mL to 10.0 g/100 mL EPA, 3.5 g/100 mL to 10.0 g/100 mL EPA, 4 g/100 mL to 10.0 g/100 mL EPA, 4.5 g/100 mL to 10.0 g/100 mL EPA, 5 g/100 mL to 10.0 g/100 mL EPA, 5.5 g/100 mL to 10.0 g/100 mL EPA, 6 g/100 mL to 10.0 g/100 mL EPA, 6.5 g/100 mL to 10.0 g/100 mL EPA, 7 g/100 mL to 10.0 g/100 mL EPA, 7.5 g/100 mL to 10.0 g/100 mL EPA, 8 g/100 mL to 10.0 g/100 mL EPA, 8.5 g/100 mL to 10.0 g/100 mL EPA, 9 g/100 mL to 10.0 g/100 mL EPA or 9.5 g/100 mL to 10.0 g/100 mL EPA.

The composition can comprise 0.5 g/100 mL to 9.5 g/100 mL EPA, 0.5 g/100 mL to 9 g/100 mL EPA, 0.5 g/100 mL to 8.5 g/100 mL EPA, 0.5 g/100 mL to 8 g/100 mL EPA, 0.5 g/100 mL to 7.5 g/100 mL EPA, 0.5 g/100 mL to 7 g/100 mL EPA, 0.5 g/100 mL to 6.5 g/100 mL EPA, 0.5 g/100 mL to 6 g/100 mL EPA, 0.5 g/100 mL to 5.5 g/100 mL EPA, 0.5 g/100 mL to 5 g/100 mL EPA, 0.5 g/100 mL to 4.5 g/100 mL EPA, 0.5 g/100 mL to 4 g/100 mL EPA, 0.5 g/100 mL to 3.5 g/100 mL EPA, 0.5 g/100 mL to 3 g/100 mL EPA, 0.5 g/100 mL to 2.5 g/100 mL EPA, 0.5 g/100 mL to 2 g/100 mL EPA, 0.5 g/100 mL to 1.5 g/100 mL EPA or 0.5 g/100 mL to 1.0 g/100 mL EPA.

Preferably the composition comprises 1.0 g/100 mL to 7.0 g/100 mL EPA. Quite especially preferable is a composition comprising 1.0 g/100 mL to 4.0 g/100 mL EPA.

The composition can comprise 0.5 g/100 mL to 10.0 g/100 mL DHA. The composition can comprise 1 g/100 mL to 10.0 g/100 mL DHA, 1.5 g/100 mL to 10.0 g/100 mL DHA, 2g/100 mL to 10.0 g/100 mL DHA, 2.5 g/100 mL to 10.0 g/100 mL DHA, 3 g/100 mL to 10.0 g/100 mL DHA, 3.5 g/100 mL to 10.0 g/100 mL DHA, 4 g/100 mL to 10.0 g/100 mL DHA, 4.5 g/100 mL to 10.0 g/100 mL DHA, 5 g/100 mL to 10.0 g/100 mL DHA, 5.5 g/100 mL to 10.0 g/100 mL DHA, 6 g/100 mL to 10.0 g/100 mL DHA, 6.5 g/100 mL to 10.0 g/100 mL DHA, 7 g/100 mL to 10.0 g/100 mL DHA, 7.5 g/100 mL to 10.0 g/100 mL DHA, 8 g/100 mL to 10.0 g/100 mL DHA, 8.5 g/100 mL to 10.0 g/100 mL DHA, 9 g/100 mL to 10.0 g/100 mL DHA or 9.5 g/100 mL to 10.0 g/100 mL DHA.

The composition can comprise 0.5 g/100 mL to 9.5 g/100 mL DHA, 0.5 g/100 mL to 9 g/100 mL DHA, 0.5 g/100 mL to 8.5 g/100 mL DHA, 0.5 g/100 mL to 8 g/100 mL DHA, 0.5 g/100 mL to 7.5 g/100 mL DHA, 0.5 g/100 mL to 7 g/100 mL DHA, 0.5 g/100 mL to 6.5 g/100 mL DHA, 0.5 g/100 mL to 6 g/100 mL DHA, 0.5 g/100 mL to 5.5 g/100 mL DHA, 0.5 g/100 mL to 5 g/100 mL DHA, 0.5 g/100 mL to 4.5 g/100 mL DHA, 0.5 g/100 mL to 4 g/100 mL DHA, 0.5 g/100 mL to 3.5 g/100 mL DHA, 0.5 g/100 mL to 3 g/100 mL DHA, 0.5 g/100 mL to 2.5 g/100 mL DHA, 0.5 g/100 mL to 2 g/100 mL DHA, 0.5 g/100 mL to 1.5 g/100 mL DHA or 0.5 g/100 mL to 1.0 g/100 mL DHA.

Preferably the composition comprises 1.0 g/100 mL to 7.0 g/100 mL DHA. Quite especially preferable is a composition containing 1.0 g/100 mL to 4.0 g/100 mL DHA.

The composition according to the invention can comprise 5 g/100 mL to 50 g/100 mL highly purified fish oil. The composition can comprise 10 g/100 mL to 50 g/100 mL highly purified fish oil, 15 g/100 mL to 50 g/100 mL highly purified fish oil, 20 g/100 mL to 50 g/100 mL highly purified fish oil, 25 g/100 mL to 50 g/100 mL highly purified fish oil, 30 g/100 mL to 50 g/100 mL highly purified fish oil, 35 g/100 mL to

50 g/100 mL highly purified fish oil, 40 g/100 mL to 50 g/100 mL highly purified fish oil, or 45 g/100 mL to 50 g/100 mL highly purified fish oil. The composition can comprise 5 g/100 mL to 45 g/100 mL highly purified fish oil, 5 g/100 mL to 40 g/100 mL highly purified fish oil, 5 g/100 mL to 35 g/100 mL highly purified fish oil, 5 g/100 mL to 30 g/100 mL highly purified fish oil, 5 g/100 mL to 25 g/100 mL highly purified fish oil, 5 g/100 mL to 20 g/100 mL highly purified fish oil, 5 g/100 mL to 15 g/100 mL highly purified fish oil, or 5 g/100 mL to 10 g/100 mL highly purified fish oil. Preferred is a composition which comprises 10 g/100 mL to 40 g/100 mL highly purified fish oil, for example 15 g/100 mL to 35 g/100 mL highly purified fish oil.

The composition can comprise EPA, DHA or a combination thereof.

Use of Omegaven® (Fresenius Kabi) as the composition according to the invention is preferred.

Together with omega-3 fatty acids, the composition can also contain further additives. Preferably, the composition according to the invention contains further additives selected from medium chain fatty acids (MCT) or iron, or a combination thereof. The inventors have surprisingly discovered that through the addition of MCT and/or iron to the composition, a synergistic effect with the omega-3 fatty acids contained in the composition according to the invention occurs, which further improves the efficacy of the composition.

The composition according to the invention can comprise 5 g/100 mL to 50 g/100 mL MCT.

The composition can comprise 10 g/100 mL - 50 g/100 mL MCT, 15 g/100 mL - 50 g/100 mL MCT, 20 g/100 mL - 50 g/100 mL MCT, 25 g/100 mL - 50 g/100 mL MCT, 30 g/100 mL - 50 g/100 mL MCT, 35 g/100 mL - 50 g/100 mL MCT, 40 g/100 mL - 50 g/100 mL MCT, or 45 g/100 mL - 50 g/100 mL MCT. The composition can comprise 5 g/100 mL - 45 g/100 mL MCT, 5 g/100 mL - 40 g/100 mL MCT, 5 g/100 mL - 35 g/100 mL MCT, 5 g/100 mL - 30 g/100 mL MCT, 5 g/100 mL - 25 g/100 mL

MCT, 5 g/100 mL - 20 g/100 mL MCT, 5 g/100 mL - 15 g/100 mL MCT, or 5 g/100 mL - 10 g/100 mL MCT. Preferred is a composition which comprises 10 g/100 mL - 40 g/100 mL MCT, for example 15 g/100 mL - 35 g/100 mL MCT.

The composition according to the invention can comprise 0.1 mg/100 mL - 0.5 mg/100 mL iron. The composition can comprise 0.15 mg/100 mL - 0.5 mg/100 mL iron, 0.2 mg/100 mL - 0.5 mg/100 mL iron, 0.25 mg/100 mL - 0.5 mg/100 mL iron, 0.3 mg/100 mL - 0.5 mg/100 mL iron, 0.35 mg/100 mL - 0.5 mg/100 mL iron, 0.4 mg/100 mL - 0.5 mg/100 mL iron or 0.45 mg/100 mL - 0.5 mg/100 mL iron. The composition can comprise 0.1 mg/100 mL - 0.45 mg/100 mL iron, 0.1 mg/100 mL - 0.4 mg/100 mL iron, 0.1 mg/100 mL - 0.35 mg/100 mL iron, 0.1 mg/100 mL - 0.3mg/100 mL iron, 0.1 mg/100 mL - 0.25 mg/100 mL iron, 0.1 mg/100 mL - 0.2 mg/100 mL iron, 0.1 mg/100 mL - 0.15 mg/100 mL iron. Preferred is a composition which comprises 0.15 mg/100 mL - 0.45 mg/100 mL iron, for example 0.2 mg/100 mL - 0.4 mg/100 mL iron.

The composition is administered prior to commencement of a cycle of chemotherapy or radiotherapy. The composition can be administered 96 hours to 24 hours prior to commencement of a cycle, more preferably 72 to 24 hours prior to commencement of a cycle Quite especially preferably, the composition is administered 48 to 24 hours prior to commencement of a cycle of chemotherapy or radiotherapy.

In addition to the administration prior to commencement of a cycle of chemotherapy or radiotherapy described above, the composition can also be administered between 24 hours and 1 hour prior to commencement of the cycle. In this, administration between 10 and 2 hours prior to commencement of the cycle is advantageous, and quite especially preferable is administration 3 hours prior to commencement of a cycle.

The composition according to the invention can in principle be administered once or several times prior to commencement of a cycle of chemotherapy or radiotherapy. In case of multiple administration, the composition can for example be administered twice, three times, four times or five times. The composition can be administered consecutively.

Usually chemotherapy or radiotherapy comprises several cycles. Here the composition can be administered prior to commencement of a cycle or prior to several cycles, in each case prior to commencement of the cycle. The composition can be administered prior to each of the cycles.

The composition can be administered consecutively on several successive days, wherein the composition is preferably administered on three successive days.

The composition can be administered parenterally, preferably intravenously.

With the composition, 5 mg to 250 mg, for example 10 mg to 250 mg EPA per kilogram bodyweight and per day can be administered. Preferably 25 mg to 250 mg EPA, 50 mg to 250 mg EPA, 75 mg to 250 mg EPA, 100 mg to 250 mg EPA, 125 mg to 250 mg EPA, 150 mg to 250 mg EPA, 175 mg to 250 mg EPA, 200 mg to 250 mg EPA, 225 mg to 250 mg EPA per kilogram bodyweight and per day can be administered. 5 mg to 10 mg EPA, 5 mg to 25 mg EPA, 5 mg to 50 mg EPA, 5 mg to 75 mg EPA, 5 mg to 100 mg EPA, 5 mg to 125 mg EPA, 5 mg to 150 mg EPA, 5 mg to 175 mg EPA, 5 mg to 200 mg EPA or 5 mg to 225 mg EPA per kilogram bodyweight and per day can be administered.

It is preferable to administer with the composition 5 mg to 100 mg EPA, for example 15 mg to 85 mg EPA, 20 mg to 80 mg EPA, 25 mg to 75 mg EPA, 30 mg to 70 mg EPA, 35 mg to 65 mg EPA, or 40 mg to 60 mg EPA per kilogram bodyweight and per day. Quite especially preferable is administration of 45 mg to 55 mg EPA, 45 mg EPA, 46 mg EPA, 47 mg EPA, 48 mg EPA, 49 mg EPA, 50 mg EPA, 51 mg EPA, 52 mg EPA, 53 mg EPA, 54 mg EPA, or 55 mg EPA per kilogram bodyweight and per day.

With the composition, 5 mg to 250 mg, for example 10 mg to 250 mg DHA per kilogram bodyweight and per day can be administered. Preferably 25 mg to 250 mg DHA, 50 mg to 250 mg DHA, 75 mg to 250 mg DHA, 100 mg to 250 mg DHA, 125 mg to 250 mg DHA, 150 mg to 250 mg DHA, 175 mg to 250 mg DHA, 200 mg to 250

mg DHA, 225 mg to 250 mg DHA per kilogram bodyweight and per day can be administered. 5 mg to 10 mg DHA, 5 mg to 25 mg DHA, 5 mg to 50 mg DHA, 5 mg to 75 mg DHA, 5 mg to 100 mg DHA, 5 mg to 125 mg DHA, 5 mg to 150 mg DHA, 5 mg to 175 mg DHA, 5 mg to 200 mg DHA or 5 mg to 225 mg DHA per kilogram bodyweight and per day can be administered.

It is preferable to administer with the composition 5 mg to 100 mg DHA, for example 15 mg to 85 mg DHA, 20 mg to 80 mg DHA, 25 mg to 75 mg DHA, 30 mg to 70 mg DHA, 35 mg to 65 mg DHA, or 40 mg to 60 mg DHA per kilogram bodyweight and per day. Quite especially preferable is administration of 45 mg to 55 mg DHA, 45 mg DHA, 46 mg DHA, 47 mg DHA, 48 mg DHA, 49 mg DHA, 50 mg DHA, 51 mg DHA, 52 mg DHA, 53 mg DHA, 54 mg DHA, or 55 mg DHA per kilogram bodyweight and per day.

With the composition, 0.025 g to 1.25 g fish oil per kilogram bodyweight and per day can be administered. For example 0.05 g to 1.25 g fish oil, 0.075 g to 1.25 g fish oil, 0.1 g to 1.25 g fish oil, 0.2 g to 1.25 g fish oil, 0.3 g to 1.25 g fish oil, 0.4 g to 1.25 g fish oil, 0.5 g to 1.25 g fish oil, 0.6 g to 1.25 g fish oil, 0.7 g to 1.25 g fish oil, 0.8 g to 1.25 g fish oil, 0.9 g to 1.25 g fish oil or 1.0 g to 1.25 g fish oil per kilogram bodyweight and per day can be administered. 1.0 g to 0.025 g fish oil, 1.0 g to 0.025 g fish oil, 0.9 g to 0.025 g fish oil, 0.8 g to 0.025 g fish oil, 0.7 g to 0.025 g fish oil, 0.6 g to 0.025 g fish oil, 0.5 g to 0.025 g fish oil, 0.4 g to 0.025 g fish oil, 0.3 g to 0.025 g fish oil, 0.3 g to 0.025 g fish oil, 0.2 g to 0.025 g fish oil, 0.1 g to 0.025 g fish oil, 0.075 g to 0.025 g fish oil or 0.05 g to 0.025 g fish oil per kilogram bodyweight and per day can be administered.

Preferred is the administration of 0.1 g to 0.7 g fish oil, 0.15 g to 0.65 g fish oil, 0.2 g to 0.6 g fish oil, 0.25 g to 0.55 g fish oil per kilogram bodyweight and per day. Quite especially preferable is the administration of 0.3 g to 0.5 g fish oil per kilogram bodyweight and per day. And likewise preferred is the administration of 0.2 g fish oil per kilogram bodyweight and per day. The fish oil can be highly purified.

Most preferable is the use of Omegaven® (Fresenius Kabi) as composition according to the invention. Omegaven® can be administered at a dosage of 0.25 mL to 12.5 mL per kg bodyweight and day. For example, 0.5 mL to 12.5 mL, 1.0 mL to 12.5 mL, 1.5 mL to 12.5 mL, 2.0 mL to 12.5 mL, 2.5 mL to 12.5 mL, 3.0 mL to 12.5 mL, 3.5 mL to 12.5 mL, 4.0 mL to 12.5 mL, 4.5 mL to 12.5 mL, 5.0 mL to 12.5 mL, 5.5 mL to 12.5 mL, 6.0 mL to 12.5 mL, 7.0 mL to 12.5, 8.0 mL to 12.5 mL, 9.0 mL to 12.5 mL, 10.0 mL to 12.5 mL, 11.0 mL to 12.5 mL, 11.5 mL to 12.5 mL or 12.0 mL to 12.5 mL Omegaven® per kg bodyweight and day can be administered. 12.0 mL to 0.25 mL, 11.5 mL to 0.25 mL, 11.0 mL to 0.25 mL, 10.0 mL to 0.25 mL, 9.0 mL to 0.25 mL, 8.0 mL to 0.25 mL, 7.0 mL to 0.25 mL, 6.0 mL to 0.25 mL, 5.5 mL to 0.25 mL, 4.0 mL to 0.25 mL, 3.5 mL to 0.25 mL, 3.0 mL to 0.25 mL, 2.5 mL to 0.25 mL, 2.0 mL to 0.25 mL, 1.5 mL to 0.25 mL, 1.0 mL to 0.25 mL, 0.75 mL to 0.25 mL, or 0.5 mL to 0.25 mL Omegaven® per kilogram bodyweight and per day can be administered.

Preferred is administration of 1.0 mL to 7.0 mL, 1.5 mL to 6.5 mL, 2.0 mL to 6.0 mL or 2.5 mL to 5.5 mL Omegaven® per kilogram bodyweight and per day. Quite especially preferable is administration of 3.0 mL to 5.0 mL Omegaven® per kilogram bodyweight and per day. Likewise preferred is the administration of 2.0 mL Omegaven® per kilogram bodyweight and per day.

With the composition, 0.07 g to 0.7 g MCT per kilogram bodyweight and per day can be administered. 0.1 g to 0.7 g MCT, 0.2 g to 0.7 g MCT, 0.25 g to 0.7 g MCT, 0.3 g to 0.7 g MCT, 0.35 g to 0.7 g MCT, 0.4 g to 0.7 g MCT, 0.45 g to 0.7 g MCT, 0.5 g to 0.7 g MCT, 0.55 g to 0.7 g MCT, 0.6 g to 0.7 g MCT or 0.65 g to 0.7 g MCT per kilogram bodyweight and per day can be administered. With the composition, 0.65 g to 0.07 g MCT, 0.6 g to 0.07 g MCT, 0.55 g to 0.07 g MCT, 0.5 g to 0.07 g MCT, 0.45 g to 0.07 g MCT, 0.4 g to 0.07 g MCT, 0.35 g to 0.07 g MCT, 0.3 g to 0.07 g MCT, 0.25 g to 0.07 g MCT, 0.2 g to 0.07 g MCT, 0.15 g to 0.07 g MCT or 0.1 g to 0.07 g MCT per kilogram bodyweight and per day can be administered.

Preferred is the administration of 0.1 g to 0.5 g MCT, 0.2 g to 0.6 g MCT, 0.3 g to 0.5 g MCT or 0.35 g to 0.45 g MCT per kilogram bodyweight and per day.

With the composition, 1 mg to 11 mg iron per day can be administered. 1 mg -10 mg iron, 1 mg -9 mg iron, 1 mg -8 mg iron, 1 mg -7 mg iron, 1 mg -6 mg iron, 1 mg - 5 mg iron, 1 mg - 4 mg iron, 1 mg - 3 mg iron, 1 mg - 2 mg iron per day can be administered. 2 mg - 11 mg iron, 3 mg - 11 mg iron, 4 mg - 11 mg iron, 5 mg - 11 mg iron, 6 mg - 11 mg iron, 7 mg - 11 mg iron, 8 mg - 11 mg iron, 9 mg - 11 mg iron, or 10 mg - 11 mg iron per day can be administered. Preferred is administration of 3 mg -9 mg iron per day.

A composition with a volume of 100 mL, comprising omega-3 fatty acids, is provided. The composition can comprise one or more different omega-3 fatty acids. Preferably the composition comprises omega-3 fatty acids selected from the group consisting of EPA, DHA, long chain and very long chain omega-3 fatty acids or a combination thereof. Particularly preferable is a composition with a volume of 100 mL, which comprises 0.5 g to 10 g EPA and/or 0.5 g to 10 g DHA. The composition can comprise fish oil, for example 5 g/100 mL to 50 g/100 mL. The composition provided can further comprise MCTs and/or iron. The composition can comprise 5 g/100 mL to 50 g/100 mL MCTs and/or 0.1 mg/100 mL - 0.5 mg/100 mL iron.

The composition provided according to the invention with a volume of 100 mL can comprise 0.5 g to 10.0 g EPA. The composition can comprise 1 g to 10.0 g EPA, 1.5 g to 10.0 g EPA, 2 g to 10.0 g EPA, 2.5 g to 10.0 g EPA, 3 g to 10.0 g EPA, 3.5 g to 10.0 g EPA, 4 g to 10.0 g EPA, 4.5 g to 10.0 g EPA, 5 g to 10.0 g EPA, 5.5 g to 10.0 g EPA, 6 g to 10.0 g EPA, 6.5 g to 10.0 g EPA, 7 g to 10.0 g EPA, 7.5 g to 10.0 g EPA, 8 g to 10.0 g EPA, 8.5 g to 10.0 g EPA, 9 g to 10.0 g EPA or 9.5 g to 10.0 g EPA.

The composition can comprise 0.5 g to 9.5 g EPA, 0.5 g to 9 g EPA, 0.5 g to 8.5 g EPA, 0.5 g to 8 g EPA, 0.5 g to 7.5 g EPA, 0.5 g to 7 g EPA, 0.5 g to 6.5 g EPA, 0.5 g to 6 g EPA, 0.5 g to 5.5 g EPA, 0.5 g to 5 g EPA, 0.5 g to 4.5 g EPA, 0.5 g to 4 g EPA, 0.5 g to 3.5 g EPA, 0.5 g to 3 g EPA, 0.5 g to 2.5 g EPA, 0.5 g to 2 g EPA, 0.5 g to 1.5 g EPA or 0.5 g to 1.0 g EPA.

Preferably, the composition comprises 1.0 g to 7.0 g EPA. Quite especially preferable is a composition comprising 1.0 g to 4.0 g EPA.

The composition provided according to the invention with a volume of 100 mL can comprise 0.5 g to 10.0 g DHA. The composition can comprise 1 g to 10.0 g DHA, 1.5 g to 10.0 g DHA, 2 g to 10.0 g DHA, 2.5 g to 10.0 g DHA, 3 g to 10.0 g DHA, 3.5 g to 10.0 g DHA, 4 g to 10.0 g DHA, 4.5 g to 10.0 g DHA, 5 g to 10.0 g DHA, 5.5 g to 10.0 g DHA, 6 g to 10.0 g DHA, 6.5 g to 10.0 g DHA, 7 g to 10.0 g DHA, 7.5 g to 10.0 g DHA, 8 g to 10.0 g DHA, 8.5 g to 10.0 g DHA, 9 g to 10.0 g DHA or 9.5 g to 10.0 g DHA.

The composition provided according to the invention with a volume of 100 mL can comprise 0.5 g to 9.5 g DHA, 0.5 g to 9 g DHA, 0.5 g to 8.5 g DHA, 0.5 g to 8 g DHA, 0.5 g to 7.5 g DHA, 0.5 g to 7 g DHA, 0.5 g to 6.5 g DHA, 0.5 g to 6 g DHA, 0.5 g to 5.5 g DHA, 0.5 g to 5 g DHA, 0.5 g to 4.5 g DHA, 0.5 g to 4 g DHA, 0.5 g to 3.5 g DHA, 0.5 g to 3 g DHA, 0.5 g to 2.5 g DHA, 0.5 g to 2 g DHA, 0.5 g to 1.5 g DHA or 0.5 g to 1.0 g DHA.

Preferably the composition comprises 1.0 g to 7.0 g DHA. Quite especially preferable is a composition comprising 1.0 g to 4.0 g DHA.

The composition provided according to the invention with a volume of 100 mL can comprise 5 g - 50 g highly purified fish oil. The composition can comprise 10 g - 50 g highly purified fish oil, 15 g - 50 g highly purified fish oil, 20 g - 50 g highly purified fish oil, 25 g - 50 g highly purified fish oil, 30 g - 50 g highly purified fish oil, 35 g - 50 g highly purified fish oil, 40 g - 50 g highly purified fish oil, or 45 g - 50 g highly purified fish oil. The composition can comprise 5 g - 45 g highly purified fish oil, 5 g - 40 g highly purified fish oil, 5 g - 35 g highly purified fish oil, 5 g - 30 g highly purified fish oil, 5 g - 25 g highly purified fish oil, 5 g - 20 g highly purified fish oil, 5 g - 15 g highly purified fish oil, or 5 g -

10 g highly purified fish oil Preferred is a composition which comprises 10 g - 40 g highly purified fish oil, for example 15 g - 35 g highly purified fish oil.

The composition can comprise EPA, DHA or a combination thereof.

The composition provided according to the invention with a volume of 100 mL can comprise 5 g to 50 g MCT. The composition can comprise 10 g to 50 g MCT, 15 g to 50 g MCT, 20 g to 50 g MCT, 25 g to 50 g MCT, 30 g to 50 g MCT, 35 g to 50 g MCT, 40 g to 50 g MCT, or 45 g to 50 g MCT. The composition can comprise 5 g to 10 g MCT, 5 g to 15 g MCT, 5 g to 20 g MCT, 5 g to 25 g MCT, 5 g to 30 g MCT, 5 g to 35 g MCT, 5 g to 40 g MCT, or 5 g to 45 g MCT. Preferred is a composition which comprises 10 g to 40 g MCT, for example 15 g to 35 g.

The composition provided according to the invention with a volume of 100 mL can comprise 0.1 mg - 0.5 mg iron. The composition can comprise 0.15 mg - 0.5 mg iron, 0.2 mg - 0.5 mg iron, 0.25 mg - 0.5 mg iron, 0.3 mg - 0.5 mg iron, 0.35 mg - 0.5 mg iron, 0.4 mg - 0.5 mg iron or 0.45 mg - 0.5 mg iron. The composition can comprise 0.1 mg - 0.45 mg iron, 0.1 mg - 0.4 mg iron, 0.1 mg - 0.35 mg iron, 0.1 mg - 0.3mg iron, 0.1 mg - 0.25 mg iron, 0.1 mg - 0.2 mg iron, 0.1 mg - 0.15 mg iron. Preferred is a composition which comprises 0.15 mg - 0.45 mg iron, for example 0.2 mg - 0.4 mg iron.

A composition with a volume of 50 mL is disclosed, which differs from the solution with a volume of 100 mL disclosed above in that it comprises only half the quantity of each ingredient which is disclosed for the composition with the volume of 100 mL.

A method is provided for administration of the composition according to the invention.

A method is provided for administration of a composition comprising omega-3 fatty acids selected from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or a combination thereof, to a patient suffering from cancer, for improving the efficacy of chemotherapy or radiotherapy and/or for the prevention or reduction of side effects caused by chemotherapy or radiotherapy, the method comprising the following steps: (a) administration of the composition prior to commencement of a cycle of chemotherapy or radiotherapy to the patient, and (b) treatment of the patient with at least one cycle of chemotherapy or radiotherapy.

The method is provided for administration of a composition comprising omega-3 fatty acids selected from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or a combination thereof, to a patient suffering from cancer, for improving the efficacy of chemotherapy or radiotherapy and/or for the prevention or reduction of side effects caused by chemotherapy or radiotherapy, the method comprising the following steps: (a) the administration of the composition prior to commencement of a cycle of chemotherapy or radiotherapy, wherein the composition is administered 96 hours to 24 hours prior to commencement of a cycle of chemotherapy or radiotherapy, preferably wherein the composition is administered 72 to 24 hours prior to commencement of a cycle of chemotherapy or radiotherapy, quite especially preferably wherein the composition is administered 48 to 24 hours prior to commencement of a cycle of chemotherapy or radiotherapy, and (b) treatment of the patient with at least one cycle of chemotherapy or radiotherapy.

The administration under step (a) can be effected once or several times, for example twice, three times, four times or five times. Under step (b), the patient can for example be treated with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 cycles of chemotherapy or radiotherapy.

The method can further comprise the step: (a)' additionally administration of the composition is also again administered between 24 and 1 hour prior to

commencement of the cycle of the chemotherapy or radiotherapy, preferably wherein the composition is administered 3 hours prior to commencement of a cycle of chemotherapy or radiotherapy. The administration under step (a)' can be effected once or several times, for example twice, three times, four times or five times.

The method can be performed such that 5 mg to 250 mg per kilogram bodyweight and per day EPA, preferably wherein 20 mg to 80 mg per kilogram bodyweight and per day EPA, most preferably wherein 40 mg to 60 mg per kilogram bodyweight and per day EPA are administered and/or that 5 mg to 250 mg per kilogram bodyweight and per day DHA, preferably wherein 20 mg to 80 mg per kilogram bodyweight and per day DHA, most preferably wherein 40 mg to 60 mg per kilogram bodyweight and per day DHA are administered.

The steps (a) and/or (a)' of the method can be repeated, wherein preferably the composition is administered consecutively on several successive days, preferably wherein the composition is administered on three successive days.

The administration of the composition can be effected parenterally, preferably intravenously.

The method can additionally comprise the step: (c) additional administration of the composition during or after a cycle of chemotherapy or radiotherapy.

The method can be used for the prevention or reduction of side effects caused by chemotherapy or radiotherapy, wherein the side effects are preferably selected from the group consisting of gastrointestinal side effects, haematological side effects, reduction in liver weight, neurotoxic side effects, side effects affecting the heart, inflammatory side effects, weight loss, limited function of the immune response, reduction of inflammation or a combination thereof.

The method can be used for the treatment of cancer diseases, wherein the cancer disease is selected from the group consisting of the group consisting of solid tumours and non-solid tumours, preferably wherein the solid tumours are selected from the group consisting of colorectal carcinoma, mammary carcinoma, pancreatic carcinoma, liver carcinoma, lung carcinoma, and gastric carcinoma.

The method can be used in patients who are receiving chemotherapy, preferably wherein the chemotherapy comprises a chemotherapeutic agent which is selected from the group consisting of 5-fluorouracil, gencitabine, doxorubicin, paclitaxel, mitomycin, cyclophosphamide, epirubicin, arabinosylcytosine, tamoxifen, irinotecan, oxaliplatin, folinic acid, cisplatin, taxane, vinca alkaloids, epipodophyllotoxins, synthetic alkaloids, cytarabine, nitrosurea, dacarbazine, fludarabine, ifosfamide, mitomycin C, tamoxifen or a combination thereof.

Particularly preferable is the method wherein the chemotherapy comprises 5-fluorouracil, quite especially preferably wherein the chemotherapy is FOLFOX or FOLFIRI.

The method can be used in patients who are receiving radiotherapy, preferably wherein the radiotherapy is selected from the group consisting of teletherapy and brachytherapy.

The composition administered by means of the method can contain further preferred additives selected from the group consisting of medium chain fatty acids and iron, or a combination thereof.

The composition administered by means of the method can contain 0.5 g/100 mL to 10.0 g /100 mL EPA and/or 0.5 g/100 mL to 10.0 g /100 mL DHA, preferably 0.7 g/100 mL to 3.5 g /100 mL EPA and/or 0.7 g/100 mL to 3.5 g /100 mL DHA. Quite especially preferably, the composition contains 1 g/100 mL to 3.1 g/100 mL EPA and/or DHA.

The values and ranges mentioned above are comprised singly and in combination. Every value of a range is individually comprised, in particular all whole number intermediate values.

Examples

Example 1: Production of composition comprising eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

a) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g

b) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g

c) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g

d) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Highly purified fish oil	5g - 50 g or 25 g

As auxiliary agents, sodium oleate, sodium hydroxide and purified water suitable for injection (*aqua ad injectionem*) are used.

Example 2: Production of composition comprising eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) with admixtures (MCT, iron).

a) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g

b) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g

c) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g

d) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
Iron	0.1 mg - 5 mg or 2.5 mg

e) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
Iron	0.1 mg - 5 mg or 2.5 mg

f) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
Iron	0.1 mg - 5 mg or 2.5 mg

g) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g
Iron	0.1 mg - 5 mg or 2.5 mg

h) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g
Iron	0.1 mg - 5 mg or 2.5 mg

i) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Eicosapentaenoic acid (EPA)	0.5 g - 5 g or 2.5 g
Docosahexaenoic acid (DHA)	0.5 g - 5 g or 2.5 g
MCT	5 g - 50 g or 25 g
Iron	0.1 mg - 5 mg or 2.5 mg

j) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Highly purified fish oil	5g - 50 g or 25 g
MCT	5 g - 50 g or 25 g

k) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Highly purified fish oil	5g - 50 g or 25 g
Iron	0.1 mg - 5 mg or 2.5 mg

l) A composition comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Highly purified fish oil	5g - 50 g or 25 g
MCT	5 g - 50 g or 25 g
Iron	0.1 mg - 5 mg or 2.5 mg

Example 3: Production of Omegaven®.

An emulsion (Omegaven®), comprising the following components (statements based on 100 mL unless otherwise stated) was produced:

Highly purified fish oil containing:	10.0 g
Eicosapentaenoic acid (EPA)	1.25g - 2.82g
Docosahexaenoic acid (DHA)	1.44g - 3.09g
Myristic acid	0.1g - 0.6g
Palmitic acid	0.25g - 1.0 g
Palmitoleic acid	0.3g - 0.9g
Stearic acid	0.05g - 0.2g
Oleic acid	0.6g - 1.3g
Linolic acid	0.1g - 0.7g
Linolenic acid	≤ 0.2g
Octadecatetraenoic acid	0.05g - 0.65g
Eicosaenoic acid	0.05g - 0.3g

Highly purified fish oil containing:	10.0 g
Arachidonic acid	0.1g - 0.4g
Docosaenoic acid	≤ 0.15g
Docosapentaenoic acid	0.15g - 0.45g
d1-α-Tocopherol	0.015g - 0.0296g
Glycerol	2.5g
Purified phosphatides from egg	1.2g
Total energy	470kJ/100 mL; 112 kcal/100 mL
pH	7.5 - 8.5
Titration acid	< 1 mmol HCl/L
Osmolarity	308 - 367 mosm/kg

As auxiliary agents, sodium oleate, sodium hydroxide and water suitable for injection (*aqua ad injectionem*) are used.

Example 4: Intravenous administration of a composition comprising EPA and DHA.

A consecutive intravenous administration of Omegaven® is effected two days and one day prior to commencement of a cycle of 5-FU based adjuvant chemotherapy in a patient with colorectal carcinoma. The chemotherapy scheme used in the patient is the so-called FOLFOX scheme. The administration of Omegaven® is effected at a dosage of 2 mL/kg patient's bodyweight and day (see also figures 1 and 3).

The intravenous administration of Omegaven® is effected each time prior to commencement of a cycle of chemotherapy comprising 12 cycles. Omegaven® is administered prior to each of the 12 cycles. Each cycle is followed by a multiday treatment pause in which the patient is given no chemotherapeutic agents, and which extends to the commencement of the next cycle of chemotherapy.

Omegaven® is in each case administered prior to commencement of a cycle, that is during the treatment pause.

A consecutive intravenous administration of Omegaven® is effected two days, one day and on the day of commencement of a cycle of a 5-FU-based adjuvant chemotherapy according to the FOLFOX scheme in a patient with colorectal carcinoma. The administration on the day of commencement of the chemotherapy cycle is effected 3 hours prior to commencement of the cycle, and is completed at the latest one hour prior to commencement of the cycle. The administration of Omegaven® is effected at a dosage of 2 mL/kg patient's bodyweight and day (see also figure 2).

Example 5: Investigation of the influence of a composition comprising EPA and DHA on the efficacy of chemotherapy and on chemotherapy-induced side effects in a murine model of human colorectal carcinoma.

For the experiment, female NMRI nu/nu mice (Elevage Janvier, Le Genest St Isle, France) aged from 7 to 8 weeks with a weight of about 25 g are used. After reception, the animals are injected with 2 x 10^6 cells/0.1 mL of the human colorectal carcinoma cell line LS174T, and kept in isolators for two weeks under standardized, specified pathogen-free conditions, and autoclaved litter and feed are used.

Two weeks after the inoculation with tumour cells, mice with tumours of about 30 mm^3 are divided into the various experimental groups. The division is effected such that average tumour volumes comparable between the groups are present.

Animals of group A 48 hours and 24 hours prior to commencement of a treatment with 5-FU each time receive an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day; corresponding to 60 µL Omegaven®/200 µL saline with a weight of 30 g). The injection is effected via the caudal vein. Animals of group B in addition to the infusion with Omegaven®, 48 hours and

24 hours, three hours prior to commencement of the treatment with 5-FU each time receive a further infusion with Omegaven®. Animals of the control group C 48 hours and 24 hours prior to commencement of the treatment with 5-FU each time receive an intravenous infusion with Lipovenous® at appropriate dosage. Animals of the control group D 24 hours and 48 hours after commencement of the treatment with 5-FU each time receive an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day). The treatment with 5-FU (50 mg/kg bodyweight and day) is effected by intraperitoneal injection on seven successive days.

Influence on the efficacy of the chemotherapy:

The tumour growth is determined by measurement of the three orthogonal tumour diameters with a sliding calliper on the basis of the formula

Tumour volume = $4\pi/3$ x (length/2 x breadth/2 x height/2).

The measurement is made every two days. Changes in the tumour volume are calculated relative to the initial tumour volume of an animal.

It is found that animals of group A and B have a lower average tumour volume compared to animals of group C and D. A trend towards a reduced tumour volume in the animals of group B compared to group A is observed.

In addition, at the end of the experiment, in a proportion of the animals the deposition of [^{125}I] in various tissues was determined by investigating the distribution of the radioactivity after two-day pretreatment with potassium iodide and perchlorate in the drinking water (to inhibit the uptake of radioactive iodine into thymus and stomach) and a single intravenous injection with 250 KBq [^{125}I]. 24 hours after the injection the animals are killed by CO_2 inhalation and the radioactivity in the tumour and in the various organs (lung, heart, liver, stomach, small intestine, large intestine, spleen and kidneys) measured in the γ counter (Cobra QC 5002, Packard, US). The organ weights are recorded.

On the basis of the comparison of the average deposition of [^{125}I] observed in the tumours of the animals of the various groups, it is clear that an administration of Omegaven prior to the commencement of chemotherapy (groups A, B) is advantageous.

Influence on the side effects of chemotherapy:

To investigate the influence of an EPA and DHA-containing composition (Omegaven®) on the side effects occurring during chemotherapy with 5-FU, at the end of the treatment with 5-FU various parameters were recorded from a proportion of the animals treated as described above, including the liver weight, the PEG_2 activity in liver homogenates (Bicyclo-PEG2 Enzyme Immunoassay Kit; Cayman Chemical, Ann Abor, MI, USA), and the scale of changes in the animals‘ intestinal tract (investigation of crypt height and apoptotic figures in formalin-fixed, paraffin wax-embedded histological preparations after haematoxylin and eosin staining), and changes in the blood profile (determination of the cell counts of the individual cellular blood components on the Cell-Dyn 3500R).

The liver weight in the animals of groups A and B is higher than that in the animals of group C, and the animals have a lower relative content of PGE_2. Compared to the control group C, in animals of groups A and B fewer changes occur in the crypt and cell structure of the normal mucous membrane of the intestine. The animals of groups A and B have a more advantageous blood profile, closer to the normal values present, than animals of the control group C.

Example 6: Investigation of the influence of EPA and DHA on the irradiation sensitivity of human colorectal cells *in vitro*.

HT-29 colorectal carcinoma cells (ATCC Number HTB-38) were cultured in Dulbeccos' modified Eagle's medium (DMEM, Ref. D 5030, Sigma Chemie AG, Buchs, Switzerland) supplemented with 10% heat-inactivated foetal calf serum (FBS), 1 g/L D-glucose, 3,7 g/L sodium bicarbonate and 0.1 g/L penicillin-

streptomycin (all additives from Life Technologies Inc., Grand Island, NY). The cells were cultured at 37°C in a humidified atmosphere with 5% CO_2 content and kept in the exponential growth phase by twice weekly subculturing. The cultures were tested for mycoplasma infection by means of the MycoAlert detection kit (Ref. LT07-118, Cambrex, Verviers, Belgium).

The cytotoxic effect of a two day (48 hour) pretreatment of HT-29 cells with 0 µM, 20 µM, 50 µM or 100 µM DHA or EPA on an irradiation of the cells with 0 Gy, 2 Gy, 4 Gy or 6 Gy was investigated in a 15-day clonogenicity experiment.

For this, the culture medium of the cells was replaced by medium which contained the respective concentrations (0 µM, 20 µM, 50 µM or 100 µM) of DHA or EPA. Controls were cultured in medium without EPA and without DHA. The cells were cultured for 48 hours in the respective medium, and then irradiated with a single radiation dose of 0 Gy (control), 2 Gy, 4 Gy or 6 Gy in an X-ray 6 MV device. The cells were then detached from the culture vessel by trypsinization (1x trypsin - EDTA, Life Technologies Inc., Grand Island, NY), resuspended and counted. The cells were thereupon serially diluted according to a standard protocol and seeded at a cell count which leads to the formation of about 200 colonies into 100 x 20 mm cell culture dishes containing 10 mL cell culture medium. After 14-day incubation at 37°C, the vessels were washed with phosphate-buffered saline (PBS, Life Technologies Inc., Grand Island, NY), fixed and stained with a 0.5% crystal violet solution in methanol/glacial acetic acid (3:1, v/v). The surviving cell fraction was calculated relative to the untreated controls (S/S0).

The results (see figure 4) of the experiment point to a synergistic effect of a dosage of 20 µM to 100 µM of the omega-3 fatty acids DHA and EPA with an irradiation of 2 to 6 Gy. (see figure 4).

Example 7: Investigation of the influence of EPA and DHA on the irradiation sensitivity of carcinoma cell lines *in vitro*.

Human carcinoma cell lines (HT-29; ATCC Number HTB-38) are cultured in Dulbeccos' modified Eagle's Medium (DMEM, Ref. D 5030, Sigma Chemie AG, Buchs, Switzerland) supplemented with 10% heat-inactivated foetal calf serum (FBS), 1 g/L D-glucose, 3,7 g/L sodium bicarbonate and 0.1 g/L penicillin-streptomycin (all additives from Life Technologies Inc., Grand Island, NY). The cells are cultured at 37°C in a humidified atmosphere with 5% CO_2 content and kept in the exponential growth phase by twice weekly subculturing. The cultures are tested for mycoplasma infection by means of the MycoAlert detection kit (Ref. LT07-118, Cambrex, Verviers, Belgium).

The cytotoxic effect of a treatment of the cells with DHA, EPA, MCT and iron on irradiation of the cells with 0 Gy, 2 Gy, 4 Gy or 6 Gy is investigated in a 15 day clonogenicity experiment.

Firstly, the influence of 0 µM, 20 µM, 50 µM or 100 µM DHA or EPA with treatment of the cells (A) prior to the irradiation in comparison to treatment of the cells after the irradiation (B) is determined. Cells not treated with EPA or DHA, which were likewise irradiated, serve as control (C).

With the cells which are treated with EPA or DHA prior to irradiation (A), the culture medium of the cells is replaced by medium with the respective concentrations (0 µM, 20 µM, 50 µM or 100 µM) of DHA or EPA. The cells are cultured for 48 hours in the medium, and then irradiated with a single radiation dose of 0 Gy (control), 2 Gy, 4 Gy or 6 Gy in an X-ray 6 MV device.

With cells which are treated with EPA or DHA after irradiation (B) and with the control cells (C), 48 hours prior to the irradiation, a medium change is performed, the cells receive normal culture medium. After 48 hours, the cells are irradiated with a single radiation dose of 0 Gy (control), 2 Gy, 4 Gy or 6 Gy in an X-ray 6 MV device.

After the irradiation, the cells are then detached from the culture vessel by trypsinization (1x trypsin - EDTA, Life Technologies Inc., Grand Island, NY), resuspended and counted. The cells are thereupon serially diluted according to a standard protocol and inoculated into 100 x 20 mm cell culture dishes with 10 mL medium in a cell count which leads to the formation of about 200 colonies. Cells of groups A and C are inoculated in normal culture medium, and cells of group B in medium with the respective concentrations (0 µM, 20 µM, 50 µM or 100 µM) of DHA or EPA.

After 48 hours, a medium change is performed with all cells, after which all cells are cultured in normal culture medium.

After a total of 14 days' incubation at 37°C, the vessels are washed with phosphate-buffered saline (PBS, Life Technologies Inc., Grand Island, NY), fixed and stained with a 0.5% crystal violet solution in methanol/glacial acetic acid (3:1, v/v). The surviving cell fraction is calculated relative to the untreated controls (S/S0).

It is found that with treatment with EPA or DHA prior to irradiation (A), fewer colonies are formed relative to the untreated controls (C) and to the cells treated after irradiation (B), and that the colonies formed are smaller. The surviving cell fraction is likewise lower.

The experiment is performed similarly with further tumour cell lines (colorectal carcinoma cell lines, mammary carcinoma cell lines and lung carcinoma cell lines). With these cell lines also, a stronger cytotoxic effect of a pretreatment with EPA or DHA is seen in comparison to post-treatment with EPA or DHA.

Example 8: Influence of administration of Omegaven® on efficacy and side effects of irradiation *in vivo*

In the first part of the experiment, the influence of Omegaven® on the efficacy of irradiation is investigated in female Balb/c nude mice (Elevage Janvier, Le Genest St Isle, France). 6 to 8 week-old animals with a weight of about 25 g are used. After reception, the animals are injected subcutaneously with 4 x 10^6 cells/0.1 mL of the human colorectal carcinoma cell line HT29, and kept in isolators for two weeks under standardized, specified pathogen-free conditions, and autoclaved litter and feed are used.

After the inoculation with tumour cells and the growth of the tumours, the mice are divided into the various experimental groups. The division is effected such that average tumour volumes comparable between the groups are present. Group A 48 and 24 prior to commencement of irradiation each time receives an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day; corresponding to 60 µL Omegaven®/200 µL saline with a weight of 30 g). The injection is effected via the caudal vein. Animals of group B, in addition to the infusion with Omegaven® 48 hours and 24 hours, three hours prior to commencement of irradiation receive a further infusion with Omegaven®. Animals of the control group C 48 hours and 24 hours prior to commencement of irradiation each time receive an intravenous infusion with Lipovenous® in corresponding dosage. Animals of the control group D 24 hours and 48 hours after commencement of irradiation each time receive an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day). The irradiation of the tumours is effected by irradiation twice with 7.5 Gy.

<u>Influence on the efficacy of irradiation:</u>

The tumour growth is determined by measurement of the three orthogonal tumour diameters with a sliding calliper on the basis of the formula

Tumour volume = $4\pi/3$ x (length/2 x breadth/2 x height/2).

The measurement is made every two days. Changes in the tumour volume are calculated relative to the initial tumour volume of an animal.

It is found that animals of group A and B have a lower average tumour volume compared to group C and D. A trend towards a reduced tumour volume is observed in the animals of group B compared to group A.

In the second part of the experiment, the influence of Omegaven® on the side effects of irradiation is investigated. The female C57 black mice used are kept as described above. The animals of group A 48 and 24 prior to commencement of irradiation each time receive an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day; corresponding to 60 µL Omegaven®/200 µL saline with a weight of 30 g). The injection is effected via the caudal vein. Animals of group B, in addition to the infusion with Omegaven® 48 hours and 24 hours receive a further infusion with Omegaven® three hours prior to commencement of irradiation. Animals of the control group C 48 hours and 24 hours prior to commencement of irradiation each time receive an intravenous infusion with Lipovenous® in appropriate dosage. Animals of the control group D 24 hours and 48 hours after commencement of irradiation each time receive an intravenous infusion with Omegaven® (2 mL/kg bodyweight and day). The irradiation of the animals is effected with a single dose of 16.5 Gy. During this, the animals are screened with lead plates so that the muzzle of the animals is selectively irradiated.

Side effects occurring after the irradiation (reactions of the epidermis and mucous membrane, oedema, weight loss) are recorded and compared between the groups. The parameters recorded comprise scale of the swelling, scale of the reddening, and scab formation.

It is found that animals of groups A and B suffer from the side effects of chemotherapy less strongly than animals of group C. The scale of the side effects is less than that observed in the animals of group D. The experiment shows a protective action of the administration of Omegaven®, which is particularly marked when Omegaven® was already administered prior to irradiation.

Patentkrav

1. Sammensetning omfattende en kombinasjon av omega-3-fettsyrene eikosapentaensyre (EPA) og dokosaheksaensyre (DHA) for bruk ved forbedring av virkeevnen til en kjemoterapi eller en radioterapi og/eller ved forebygging eller reduksjon av bivirkninger forårsaket av kjemoterapi eller radioterapi hos en kreftsyk pasient, hvor sammensetningen gis parenteralt til pasienten kun 48 til 24 timer før innledning av en kjemoterapi- eller radioterapisyklus, hvor sammensetningen omfatter 1,0 g/100 mL til 7,0 g/100 mL EPA og 1,0 g/100 mL til 7,0 g/100 mL DHA.

2. Sammensetning for bruk ifølge krav 1, hvor bivirkningene er valgt fra gruppen bestående av gastrointestinale bivirkninger, hematologiske bivirkninger, tap av levervekt, nevrotoksiske bivirkninger, bivirkninger som påvirker hjertet, inflammatoriske bivirkninger, vekttap, begrenset funksjon av immunresponsen, reduksjon av inflammasjoner eller en kombinasjon derav.

3. Sammensetning for bruk ifølge ett av de foregående krav, hvor kreftsykdommen er valgt fra gruppen bestående av faste tumorer og ikke-faste tumorer, hvor de faste tumorene fortrinnsvis er valgt fra gruppen bestående av kolorektal karsinom, brystkarsinom, pankreaskarsinom, leverkarsinom, lungekarsinom og gastrisk karsinom.

4. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor kjemoterapien omfatter et kjemoterapeutikum valgt fra gruppen bestående av 5-fluoruracil, gemcitabin, doksorubicin, paklitaksel, mitomycin, syklofosfamid, epirubicin, arabinosylcytosin, tamoksifen, irinotekan, oksaliplatin, folinsyre, cisplatin, taksan, vinca-alkaloider, epipodofyllotoksiner, syntetiske alkaloider, cytarabin, nitrosourea, dakarbazin, fludarabin, ifosfamid, mitomycin C, tamoksifen eller en kombinasjon derav.

5. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor kjemoterapien omfatter 5-fluoruracil, hvor kjemoterapien fortrinnsvis er FOLFOX eller FOLFIRI.

6. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor radioterapien er valgt fra gruppen bestående av teleterapi og brachyterapi.

7. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor sammensetningen omfatter ytterligere foretrukne additiver valgt fra gruppen bestående av mellomkjedede fettsyrer og jern, eller en kombinasjon derav.

8. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor sammensetningen omfatter 1,0 g/100 mL til 4,0 g/100 mL EPA og 1,0 g/100 mL til 4,0 g/100 mL DHA.

9. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor sammensetningen i tillegg også blir administrert mellom 24 timer og 1 time før innledning av kjemoterapi- eller radioterapisyklusen, hvor sammensetningen fortrinnsvis blir administrert 3 timer før innledning av en kjemoterapi- eller radioterapisyklus.

10. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor administrering av sammensetningen blir gjentatt, hvor sammensetningen fortrinnsvis blir administrert 2 til 5 ganger.

11. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor sammensetningen blir administrert før hver kjemoterapi- eller radioterapisyklus.

12. Sammensetning for bruk ifølge ethvert av de foregående krav, hvor 5 mg til 250 mg EPA per kilo kroppsvekt og per dag blir administrert, fortrinnsvis hvor 20 mg til 80 mg EPA per kilo kroppsvekt og per dag blir administrert, mest foretrukket hvor 40

mg til 60 mg EPA per kilo kroppsvekt og per dag blir administrert, og hvor 5 mg til 250 mg DHA per kilo kroppsvekt og per dag blir administrert, fortrinnsvis hvor 20 mg til 80 mg DHA per kilo kroppsvekt og per dag blir administrert, mest foretrukket hvor 40 mg til 60 mg DHA per kilo kroppsvekt og per dag blir administrert.

Figure 1

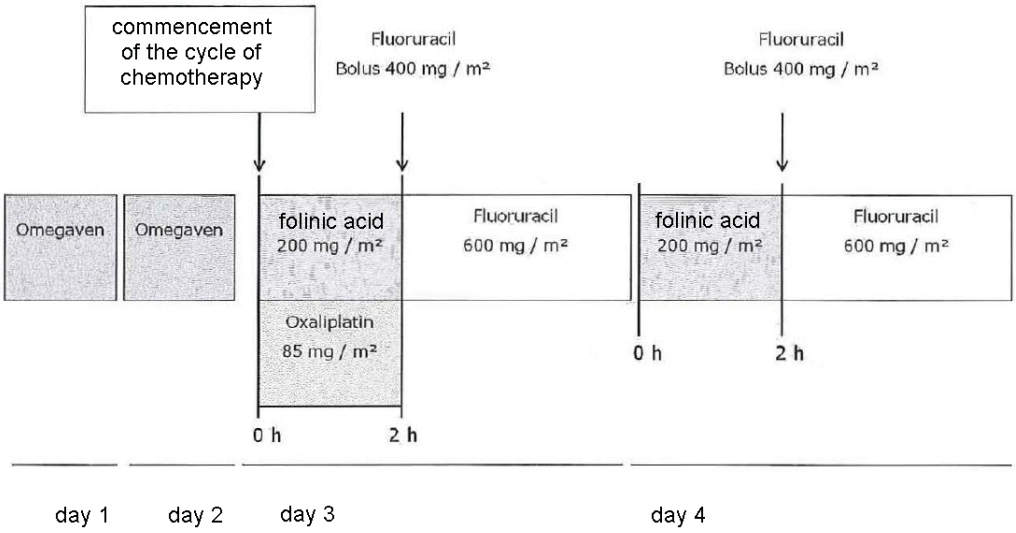

commencement of the cycle of chemotherapy
Fluoruracil
Bolus 400 mg / m²
Fluoruracil
Bolus 400 mg / m²
Omegaven
Omegaven
folinic acid
200 mg / m²
Fluoruracil
600 mg / m²
folinic acid
200 mg / m²
Fluoruracil
600 mg / m²
Oxaliplatin
85 mg / m²
0 h
2 h
0 h
2 h
day 1
day 2
day 3
day 4

Figure 2

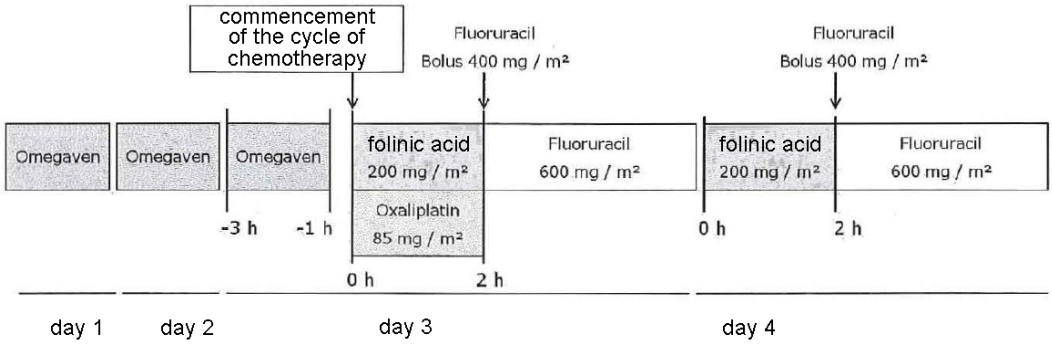

commencement of the cycle of chemotherapy
Fluoruracil Bolus 400 mg / m²
Fluoruracil Bolus 400 mg / m²
Omegaven
Omegaven
Omegaven
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
Oxaliplatin 85 mg / m²
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
-3 h
-1 h
0 h
2 h
0 h
2 h
day 1
day 2
day 3
day 4

Figure 3

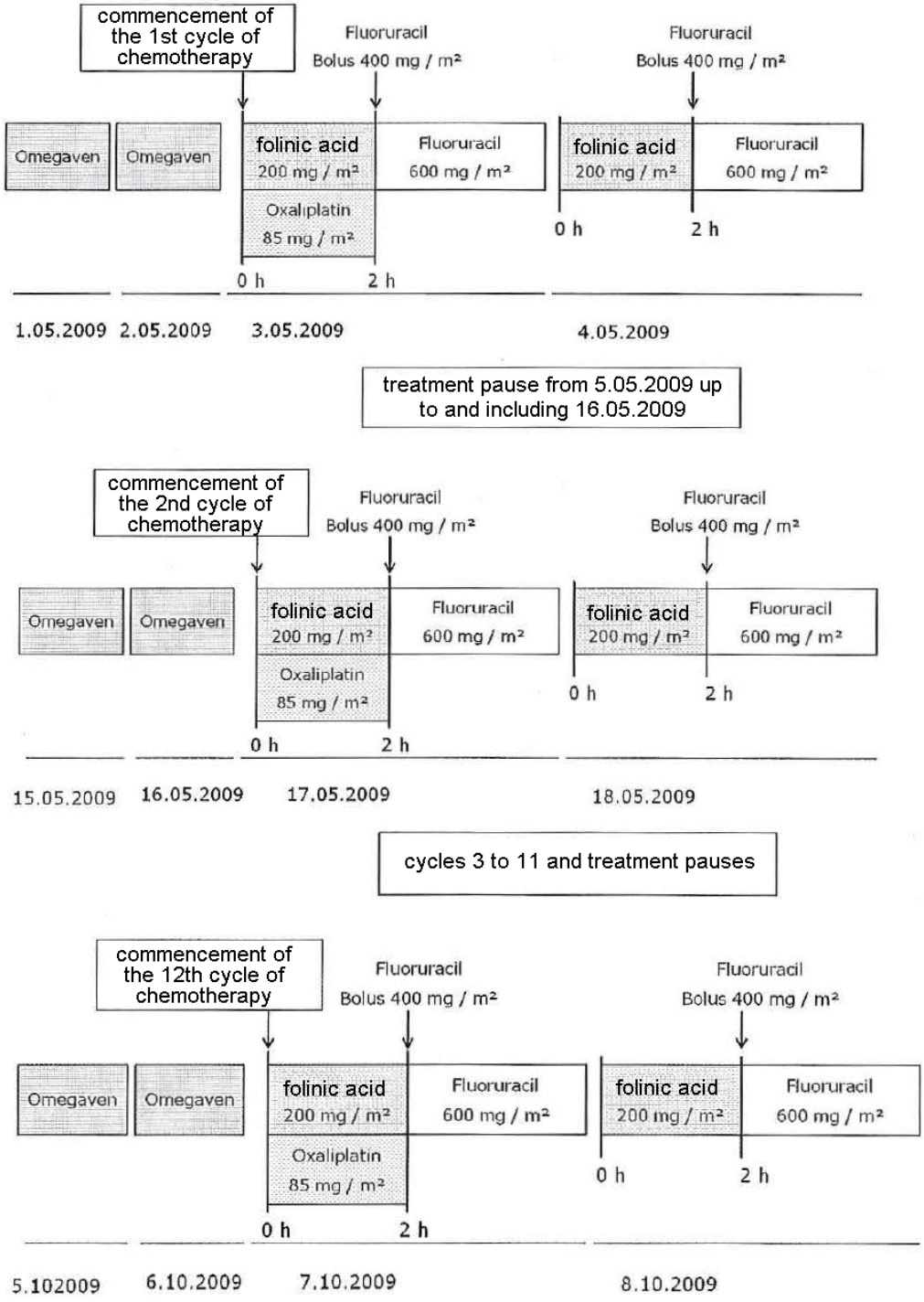
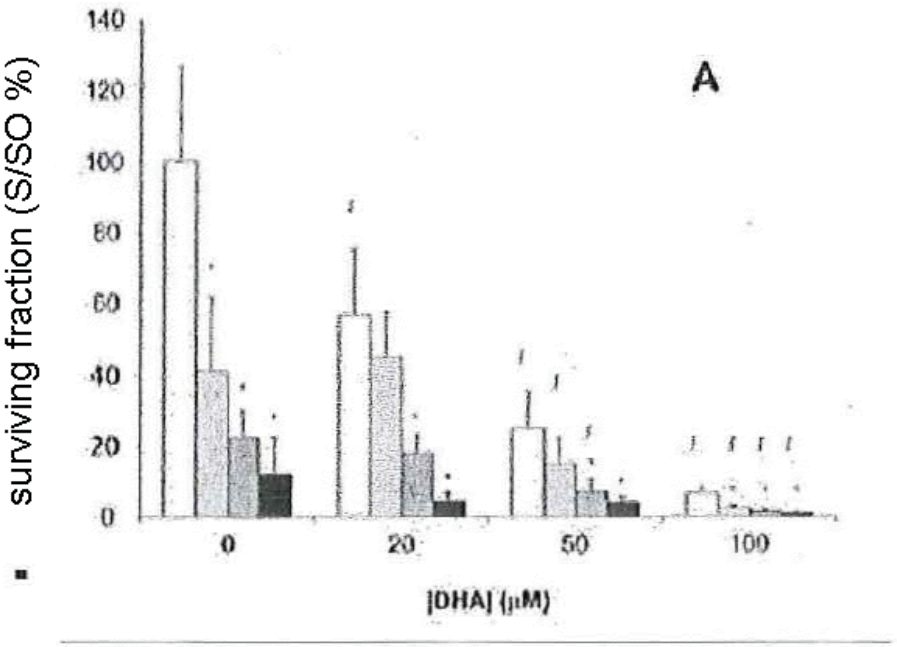
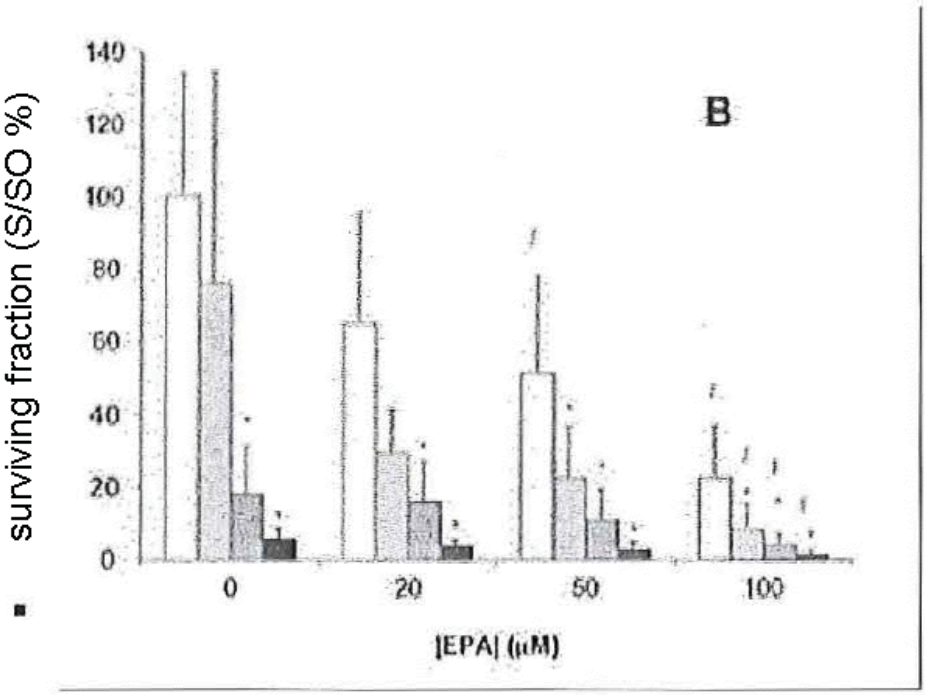

commencement of the 1st cycle of chemotherapy
Fluoruracil Bolus 400 mg / m²
Fluoruracil Bolus 400 mg / m²
Omegaven
Omegaven
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
Oxaliplatin 85 mg / m²
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
0 h
2 h
0 h
2 h
1.05.2009
2.05.2009
3.05.2009
4.05.2009
treatment pause from 5.05.2009 up to and including 16.05.2009
commencement of the 2nd cycle of chemotherapy
Fluoruracil Bolus 400 mg / m²
Fluoruracil Bolus 400 mg / m²
Omegaven
Omegaven
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
Oxaliplatin 85 mg / m²
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
0 h
2 h
0 h
2 h
15.05.2009
16.05.2009
17.05.2009
18.05.2009
cycles 3 to 11 and treatment pauses
commencement of the 12th cycle of chemotherapy
Fluoruracil Bolus 400 mg / m²
Fluoruracil Bolus 400 mg / m²
Omegaven
Omegaven
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
Oxaliplatin 85 mg / m²
folinic acid 200 mg / m²
Fluoruracil 600 mg / m²
0 h
2 h
0 h
2 h
5.102009
6.10.2009
7.10.2009
8.10.2009

Figure 4


A
surviving fraction (S/SO %)
140
120
100
80
60
40
20
0
0
20
50
100
[DHA] (μM)


B
surviving fraction (S/SO %)
140
120
100
80
60
40
20
0
0
20
50
100
[EPA] (μM)