USE OF DOCETAXEL/DOXORUBICIN/CYCLOPHOSPHAMIDE IN ADJUVANT THERAPY OF BREAST AND OVARIAN CANCER

DESCRIPTION OF THE INVENTION

Field of the Invention

This invention relates to a novel therapeutic combination of taxotere with other antineoplastic agents which are useful in the adjuvant therapy of metastatic breast and ovarian cancer.

Background of the Invention

The present invention relates more specifically to the use of docetaxel in combination with doxorubicin and cyclophosphamide as adjuvant therapy in the treatment of cancer after surgery or other first line therapy.

Selected term definitions used herein and in Tables 1-36 are as follows:

"Adjuvant therapy" refers to chemotherapy started within but no greater than 60 days from surgery.

"AT" refers to Adriamycin/Taxotere;

"docetaxel" refers to the active ingredient of TAXOTERE® or TAXOTERE® itself;

"doxorubicin" refers to the active ingredient of ADRIAMYCIN® or ADRIAMYCIN® itself.

"ER" refers to estrogen receptor;

"FAC" refers to the combination of 5-fluorouracil, doxorubicin and cyclophosphamide;

"HER2" refers to is a transmembrane receptor tyrosine kinase with partial homology with the epidermal growth factor 2 receptor, both of which receptors belong to the type 1 tyrosine kinase receptor superfamily;

"KPS" refers to Karnovsky Performance Status which is an index of a patient's physical condition;

"MF" refers to Methotrexate/5-Fluorouracil;

"MV" refers to Mitomycin/Vinblastin combination;

"PR" refers to progesterone receptor;

"TAC" refers to the combination of TAXOTERE© (docetaxel), ADRIAMYCIN (doxorubicin) and cyclophosphamide;

and

"drug" or "drugs" refers to the above-mentioned active ingredients or medicaments or pharmaceutical preparations containing them.

Previous researchers have noted that docetaxel (TAXOTERE®) and its derivatives (such as TAXOL®, paclitaxel) are useful in the treatment of malignant neoplasms, such as solid tumors and other malignancies. European Patent EP 0 253 738 and International Patent Application WO 92/09589 describe a method of preparation of docetaxel. Generally, the doses, which vary depending on the patient, comprise between 60 and 400 mg/m^2 of docetaxel. Commonly, docetaxel is administered via intravenous route at doses of 60 to 100 mg/m^2 over 1 hour every 3 weeks (*Textbook of Medical Oncology*, Franco Cavelli et al., Martin Dunitz Ltd., p. 4623 (1997)).

Many clinical studies have confirmed the efficacy of docetaxel in treating many types of cancer, particularly breast, non-small cell lung, and ovarian cancer. Docetaxel's effects are shown in both first and second line therapies. The mechanism of docetaxel's action is thought to be via enhancement of microtubule assembly and inhibition of the depolymerization of tubulin at the cellular level.

However, all treatments based on taxoid derivatives, including docetaxel, can show serious and troubling toxicities, such as myelosuppression, neutropenia, hypersensitivity, peripheral neuropathy, and fluid retention, among others (Fumoleau et al., *Bull. Cancer*, (82)8: 629-636 (1995)). When such toxicities appear, dosages of the drugs must be limited with a resulting limitation on the efficacy of the treatment.

Consequently, there is an unmet need in the art for pharmaceutical preparations and methods of treating cancer which enhance the activity of docetaxel without increasing the amount of the dosages administered and without increasing adverse side effects.

There is also an unmet need in the art for treatment of cancer which has spread beyond the initial tumor site. In metastatic breast and ovarian cancer

especially, there is a need for effective post-surgery adjuvant therapy, which will result in disease free survival or at least, an extension of the duration of progression free survival.

In recent studies, docetaxel containing regimens have shown superior activity over standard regimens in metastatic breast cancer. Anthracycline-based regimens, using e.g. doxorubicin, are standard adjuvant therapy in node positive breast cancer patients. Therefore, considering the efficacy of both docetaxel and doxorubicin in treating advanced breast cancer and their potential noncross-resistance, it was decided to combine them with cyclophosphamide as a possible design for a more effective adjuvant therapy for metastatic breast cancer. The combination of the docetaxel, doxorubicin, and cyclophosphamide (TAC) was tested in a phase III trial in 20 countries by more than 112 investigators. The results which are elaborated below show that the combination used as adjuvant therapy enhances the effect of docetaxel without increasing its dosage and results in increased survival for metastatic breast cancer patients.

SUMMARY OF THE INVENTION

In an aspect of the present invention , there is provided a use of docetaxel in the manufacture of a medicament for treating metastatic breast ovarian cancer by adjuvant therapy in combination with doxorubicine and cyclophosphamide only and which provides an increased survival rate.

Disclosed herein are methods for treating metastatic cancer, especially metastatic breast cancer and ovarian cancer, comprising administering docetaxel, doxorubicin and cyclophosphamide (TAC) in amounts effective to reduce or eliminate the presence of cancer. The efficacy of this combination has been demonstrated over a period of thirty-three months in more than seven hundred human patients who demonstrated positive nodal involvement and were treated post-surgery with TAC.

Disclosed herein are new pharmaceutical kits and medicaments comprising docetaxel in combination with doxorubicin and cyclophosphamide for treating cancers.

Further disclosed herein are schedules of administration of TAC for the adjuvant treatment of cancer wherein the individual drugs in the TAC combination are infused separately on the same day, once every three weeks. This cycle is repeated six times.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The inventors of the present invention have demonstrated via clinical trials, that TAC dosages in particular manifest an unexpected and strong therapeutic effect on the treatment of neoplastic diseases, particularly breast cancers, and more particularly, in metastatic breast cancers in which ER/PR and HER2 are overexpressed. Generally, according to the invention, docetaxel is administered in a dosage of 75 mg/m^2, doxorubicin in a dosage of 50 mg/m^2 and cyclophosphamide in a dosage of 500 mg/m^2, once every three weeks. This cycle is generally repeated six times.

Docetaxel alone, in several in-house proprietary studies, gave overall response rates of 40 to 43% (in second line therapy at a dose of 100 mg/m^2), 48% (in first line therapy at a dose of 75 mg/m^2) and 61°/a (in first line therapy at a dose of 100 mg/m^2).

In comparison, in the example below, 75 mg/m^2 of docetaxel administered in combination with 50 mg/m^2 doxorubicin and 500 mg/m^2 cyclophosphamide resulted in an 82% response rate.

According to the invention, the new use of docetaxel as a component of TAC is very advantageous for treating cancers of the breast, ovary, and lung; still more preferably, the new use of docetaxel is particularly suitable for treating metastatic breast cancer.

The safety and the efficacy of the combination of docetaxel, doxorubicin and cyclophosphamide was tested in patients according to the following protocol:

Patients were eligible for the study if they had histologically proven breast cancer, definitive surgery with axillary lymph node dissection (greater than or equal to 6 lymph nodes), a period of 60 days or less between surgery and randomization, stage 1 to 3 cancer, at least one node that was positive for cancer, were 70 years old or less, had a KPS index greater than or to 80% and had normal bone marrow, liver, renal and cardiac function. *See* Table 4.

One thousand, four hundred and ninety-one patients were accepted into the study. Seven hundred and forty-five received TAC as adjuvant therapy and seven hundred and forty-six received FAC. The TAC patients had a median age of 49

years, 51 % were premenopausal, and 60% percent had had a mastectomy. Sixty-eight % had had radiotherapy and 68% had taken tamoxifen. The patient characteristics for the FAC group were similar (*See* Table 6).

Of the seven hundred and forty-five TAC patients, 62% had 1-3 cancer-positive nodes, 30% had 4 to 10 positive nodes and 8% had more than 10 positive nodes. In 40% of the patients, the size of the tumor was 2 cm or less, in 53%, the size of the tumor was more than 2 cm but equal to or less than 5 cm., and in 7 % of the patients, the tumor was larger than 5 cm. Sixty-nine per cent of the patients had overexpressing ER or PR tumors and 19% had overexpressing HER2 + (FISH) tumors. Again, the tumor characteristics of the FAC group were comparable. *See* Table 7.

The primary endpoint of this Phase III study was to facilitate disease free survival while secondary endpoints were overall survival, toxicity, quality of life and monitoring pathological and molecular markers.

Post-TAC and post-FAC treatment included 1) radiation therapy for all patients with breast conserving surgery and 2) tamoxifen (20 mg/day for 5 years) for those patients with ER or PR positive tumors. *See* Table 3.

The Example below illustrates the new use of docetaxel according to the invention without limiting it.

EXAMPLE:

Dexamethasone, 8 mg BID was given as a premedication for 3 days. The combination adjuvant therapy was then administered on Day 4. One group of patients received docetaxel, doxorubicin and cyclophosphamide (TAC) administered intravenously in that order. Another group of patients received 5-FU, doxorubicin, and cyclophosphamide (FAQ administered intravenously in that order. Prophylactic Cipro was then given to both groups on days 5-14 in a dose of 500 mg BID. This course of drugs was repeated every three weeks for six cycles. *See* Table 2.

Six hundred and seventy-nine patients (91%) completed six cycles of TAC adjuvant therapy followed by the postchemical therapy regimens described above.

The median total dose per patient over the six cycles was 446 mg/m^2 of docetaxel, 297 mg/m^2 of doxorubicin, and 2978 mg/m^2 of cyclophosphamide. *See* Table 8.

Seven hundred and eleven patients (96%) completed six cycles of FAC adjuvant therapy followed by the postchemical therapy regimens described above. The median total dose per patient over the six cycles was 2985 mg/m^2 of 5-FU, 298 mg/m^2 of doxorubicin, and 2985 mg/m^2 of cyclophosphamide. Id.

Thirty-three months after adjuvant therapy, 82% of the TAC group vs. 74% of the FAC group were alive and disease free (Table 10). At the same time, the overall survival of the TAC group was 92% vs. 87% for the FAC group (Table 13).

Results by Nodal Status

If disease free survival of the TAC and FAC groups is compared by nodal status, 90% of patients with 1-3 positive nodes who received TAC were alive and disease free at 33 months after therapy vs. 79% of the FAC group. There was no statistical difference between the two adjuvant therapies in patients with 4 nodes, although 69% of patents receiving TAC therapy were alive and disease free at 36 months compared to 67% who received FAC. *See* Table 15.

The overall survival rate for patients with 1-3 positive nodes was 96% for TAC and 89% for FAC. Again, there was no statistical difference between the two therapies in patients with 4 or more positive nodes, although again more TAC patients (86%) survived than FAC patients (84%). *See* Tables 16 and 32.

Results by Hormonal Status

In patients with negative ER/PR tumors, the disease free survival rate was about 70% in those who had received TAC adjuvant therapy and about 62% in those receiving FAC. In patients with positive ER/PR nodes, the disease free survival rate among those who received TAC was about 88% vs. 82% in those who received FAC. *See* Tables 17 and 33.

If one calculates overall survival by hormonal status, about 83% of TAC recipients with negative ER/PR tumors survived vs. about 72% of FAC recipients. Among patients with positive tumors, about 90% of TAC recipients survived vs. about 88% of FAC recipients. *See* Tables 18 and 35.

Results by HER2 Status

In patients with negative HER2 tumors, the disease free survival rate at 33 months was about 86% in those who had received TAC adjuvant therapy and about 80% in those receiving FAC. In patients with positive HER2 tumors, the disease free survival rate among those who received TAC was about 75% vs. 60% in those who received FAC. *See* Table 19.

Based on this data, the combination of docetaxel, doxorubicin and cyclophosphamide as adjuvant therapy is well-tolerated and results in a significant advantage over 5FU, doxorubicin and cyclophosphamide as adjuvant therapy. If one measures disease free survival, at 33 months, TAC provided over FAC a 32% reduction in deaths overall, a 50% reduction in deaths where the patients had 1-3 positive nodes, a 38% reduction in deaths where the hormonal status of the tumor was negative and a 32% reduction where the hormonal status was positive. *See* Table 22.

If one measures overall survival, there was a 24% reduction in deaths of those receiving TAC adjuvant therapy and a 54% reduction in those patients with 1 to 3 positive nodes. Id.

The difference between TAC and FAC is the presence of docetaxel rather than 5-FU. These statistics prove conclusively that the observed benefit of docetaxel in combination with doxorubicin and cyclophophamide is large enough to be of clinical value in the adjuvant treatment of node positive breast cancer patients.

The described embodiments are to be considered in all respects as illustrative only and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

1. Use of docetaxel in the manufacture of a medicament for treating metastatic breast or ovarian cancer by adjuvant therapy in combination with doxorubicine and cyclophosphamide only and which provides an increased survival rate.

2. Use according to claim 1 wherein docetaxel, doxorubicin and cyclophosphamide are suitable for administration separately.

3. Use according to claim 1 wherein the medicament is for treating metastatic breast cancer.

4. Use according to claim 3 wherein the said breast cancer ER, PR and/or HER2 are overexpressed.

5. Use according to claim 2 wherein docetaxel, doxorubicin and cyclophosphamide are suitable for administration once every 3 weeks.

6. Use according to claim 2 wherein docetaxel is suitable for administration at a dose of approximately 75 mg/m2 per cycle.

7. Use according to claim 2 wherein doxorubin is suitable for administration at a dose of approximately 50 mg/m2 per cycle.

8. Use according to claim 2 wherein cyclophosphamide is suitable for administration at a dose of approximately 500 mg/m2 per cycle