where cancer has evolved into a widespread systemic disease), or from a liquid cancer, in the context of radiotherapy, preferably in the context of a fractionated radiotherapy.

A typical composition is a vaccine composition comprising a nanoparticle and/or aggregate of nanoparticles for use for treating cancer in a subject suffering from metastatic cancer and undergoing a palliative radiotherapy, in a subject suffering from metastatic cancer for whom (curative) radiotherapy has been abandoned, in a subject suffering from a cancer which is not (conventionally) treated by radiotherapy, or in a subject suffering from a liquid cancer, wherein the treatment comprises exposing the subject to a fractionated radiotherapy comprising at least one irradiation step wherein the ionizing radiations dose ranges from 1.8 to 30 Gray (Gy), preferably 1.8 to 20 Gray (Gy), and wherein each nanoparticle consists in a material having a density of at least 7 g/cm^3 and an atomic number (Z) of at least 25 and each nanoparticle or aggregate of nanoparticles is covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid.

In one aspect of the disclosure, there is provided a use of a nanoparticle and/or aggregate of nanoparticles for preparing a vaccine composition for treating cancer in a human subject suffering from metastatic cancer and undergoing a palliative radiotherapy, in a human subject suffering from metastatic cancer for whom radiotherapy has been abandoned, in a human subject suffering from a cancer which is not treated by radiotherapy, or in a human subject suffering from a liquid cancer affecting blood or lymphoid cell tissue; wherein said human subject, or a cancer sample from said human subject comprising the nanoparticle and/or aggregate of nanoparticles; is to be exposed to a fractionated radiotherapy comprising at least one irradiation step wherein the ionizing radiations dose ranges from 1.8 to 30 Gray (Gy), and wherein each nanoparticle consists in a material having a density of at least 7 g/cm^3 and an atomic number (Z) of at least 25 and each nanoparticle or aggregate of nanoparticles is covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid.

The vaccine composition comprises a nanoparticle or aggregate of nanoparticles as herein described preferably together with a pharmaceutically acceptable carrier or vehicle. A particular vaccine composition further comprises at least one immunotherapeutic agent and optionally a therapeutic agent for treating cancer.

Also herein described is the use of a nanoparticle or aggregate of nanoparticles or a therapeutic composition as herein defined for treating cancer in a subject, preferably in selected populations of subjects/patients, typically in a subject suffering from metastatic cancer and undergoing a palliative radiotherapy, in a subject suffering from metastatic cancer for whom (curative) radiotherapy has been abandoned, in a subject suffering from a cancer which is not (conventionally) treated by radiotherapy, or in a subject suffering from a liquid cancer, as well as the corresponding methods for treating cancer

in a subject in need thereof comprising a step of administering to said subject a nanoparticle or aggregate of nanoparticles or a therapeutic composition as herein defined.

In yet another aspect of the disclosure there is provided a use of a nanoparticle and/or aggregate of nanoparticles for preparing a vaccine composition for treating cancer in a human subject suffering from a metastatic cancer or from a liquid cancer affecting blood or lymphoid cell tissue, wherein said human subject, or a cancer sample from said human subject comprising the nanoparticle and/or aggregate of nanoparticles; is to be exposed to fractionated radiotherapy comprising at least one irradiation step wherein the ionizing radiations dose ranges from 1.8 to 20 Gray (Gy), and wherein each nanoparticle consists in a material having a density of at least 7 g/cm3 and an atomic number (Z) of at least 25 and each nanoparticle or aggregate of nanoparticles is covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid

Further herein provided is a kit, typically a vaccine kit, comprising (i) a nanoparticle or aggregate of nanoparticles as herein described, or a composition comprising such a nanoparticle or aggregate of nanoparticles, preferably together with (ii) at least one immunotherapeutic agent and/or therapeutic agent for treating cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: HMGB1 released in the concentrated cell supernatant from cells treated or not with HfO_2 nanoparticles (NPs) suspension from example 1 and exposed or not to radiotherapy (5 Gy delivered in a single fraction) is reported as fold-change in comparison to untreated control.

CLAIMS

1. Use of a nanoparticle and/or aggregate of nanoparticles for preparing a vaccine composition for treating cancer in a human subject suffering from a metastatic cancer or from a liquid cancer affecting blood or lymphoid cell tissue; wherein said human subject, or a cancer sample from said human subject comprising the nanoparticle and/or aggregate of nanoparticles; is to be exposed to a fractionated radiotherapy comprising at least one irradiation step wherein the ionizing radiations dose ranges from 1.8 to 20 Gray (Gy), and wherein each nanoparticle consists in a material having a density of at least 7 g/cm^3 and an atomic number (Z) of at least 25 and each nanoparticle or aggregate of nanoparticles is covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid.

2. Use of a nanoparticle and/or aggregate of nanoparticles for preparing a vaccine composition for treating cancer in a human subject suffering from metastatic cancer and undergoing a palliative radiotherapy, in a human subject suffering from metastatic cancer for whom radiotherapy has been abandoned, in a human subject suffering from a cancer which is not treated by radiotherapy, or in a human subject suffering from a liquid cancer affecting blood or lymphoid cell tissue; wherein the human subject, or a cancer sample of said human subject comprising the nanoparticle and/or aggregate of nanoparticles; is to be exposed to a fractionated radiotherapy comprising at least one irradiation step wherein the ionizing radiations dose ranges from 1.8 to 30 Gray (Gy), and wherein each nanoparticle consists in a material having a density of at least 7 g/cm^3 and an atomic number (Z) of at least 25 and each nanoparticle or aggregate of nanoparticles is covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid.

3. The use according to claim 2 wherein the ionizing radiations dose ranges from 1.8 to 20 Gray (Gy).

4. The use according to anyone of claims 1 to 3 wherein, when the cancer is a metastatic cancer, the at least one irradiation step is to be applied *in vivo* on one, at most two, tumor sites of the metastatic cancer comprising the nanoparticles or aggregates of nanoparticles.

5. The use according to anyone of claims 1 to 3 wherein, when the cancer is a metastatic cancer, the at least one irradiation step is to be applied *ex vivo* on a cancer sample of the subject comprising the nanoparticles or aggregates of nanoparticles, and the *ex vivo* lethally irradiated cancer cells and at least part of the associated cell supernatant from the cancer sample are to be at least partly readministered to the subject before any optional subsequent *in vivo* treatment of cancer in said subject.

6. The use according to anyone of claims 1 to 3 wherein, when the cancer is a liquid cancer, the at least one irradiation step is to be applied *ex vivo* on a liquid cancer sample of the subject comprising the nanoparticles or aggregates of nanoparticles, and the irradiated liquid cancer sample is to be at least partly readministered to the subject before any optional subsequent *in vivo* treatment of cancer in said subject.

7. The use according to claim 6 wherein the liquid cancer sample is a blood sample or the whole blood volume of the subject.

8. The use according to anyone of claims 5 to 7, wherein the *ex vivo* lethally irradiated cancer cells or the irradiated liquid cancer sample is to be at least partly readministered to the subject together with at least one additional immunotherapeutic agent; wherein the *ex vivo* lethally irradiated cancer cells or the irradiated liquid cancer sample and the least one additional immunotherapeutic agent are to be administered to the subject either simultaneously or separately.

9. The use according to anyone of claims 1 to 8, wherein the ionizing radiations dose is selected from 1.8, 2, 2.4, 2.5, 3, 3.2, 3.6, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 15 and 20 Gy per fraction treatment.

10. The use according to anyone of claims 1 to 9, wherein the metastatic cancer affects (i) a connective tissue and is selected from a fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, chordoma, malignant fibrous histiocytoma, (ii) an endothelium or mesothelium tissue and is selected from hemangiosarcoma, angiosarcoma, lymphangiosarcoma and mesothelioma, (iii) a muscle tissue and is selected from leiomyosarcoma and rhabdomyosarcoma, (iv) an epithelial tissue and is selected from adenocarcinoma, squamous cell carcinoma and epidermoid carcinoma, (v) a neural tissue and is selected from multiform glioblastoma, glioma, neuroblastoma, medulloblastoma, meningioma, neurofibrosarcoma and schwannoma, and (vi) the APUD system and is selected from thyroid carcinoma, pancreas carcinoma, stomach carcinoma and intestine carcinoma; or wherein the metastatic cancer is a melanoma.

11. The use according to claim 10 wherein the metastatic cancer is or derives from a cancer selected from skin cancer, central nervous system cancer, head and neck cancer, lung cancer, kidney cancer, breast cancer, gastrointestinal cancer (GIST), prostate cancer, liver cancer, colon cancer, rectum cancer, anal cancer, oesophagus cancer, male genitourinary cancer, gynecologic cancer, adrenal and retroperitoneal cancer, sarcomas of bone and soft tissue, pediatric cancer, neuroblastoma, central nervous system cancer and Ewing's sarcoma.

12. The use according to anyone of claims 1 to 9, wherein the liquid cancer is selected from leukemia, myeloma and lymphoma.

13. The use according to anyone of claims 1 to 12, wherein the nanoparticle or aggregate of nanoparticles are to be administered to the subject to be treated together with at least one immunotherapeutic agent, the nanoparticle or aggregate of nanoparticles and the at least one immunotherapeutic agent being administered to the subject either simultaneously or separately.

14. The use according to anyone of claims 1 to 13, wherein the composition further comprises a pharmaceutically acceptable carrier or vehicle.

15. The use according to claim 14, wherein the composition further comprises at least one immunotherapeutic agent.

16. A kit comprising (i) a nanoparticle or aggregate of nanoparticles consisting in a material having a density of at least 7 g/cm^3 and an atomic number (Z) of at least 25, each nanoparticle or aggregate of nanoparticles being covered with a biocompatible coating allowing the nanoparticle stability between pH 6.5 and 7.5 in a physiological fluid, or a composition as described in anyone of claims 1-14, together with (ii) at least one immunotherapeutic agent.

17. The use according to claim 15 or the kit according to claim 16, wherein the at least one immunotherapeutic agent is selected from a monoclonal antibody, a cytokine, and a combination thereof.