Oncol. (2012) 8(9), 1167–118]. Thus, radioenhancers are designed to enhance the delivery of RT precisely at the tumor site, to further optimize the benefit / risk ratio of existing treatments involving RT.

Despite the above-described efforts to optimize the benefit/risk ratio of cancer treatment and the establishment of the most appropriate treatments for patients, according to their particular cancer type and clinical stage, there remains a critical unmet need for treating patients who have been, up to now, identified as unable to undergo such standard-of-care treatments, or who are identified as being at "high risk" to undergo such standard-of-care treatments. Patients unable to undergo standard-of-care treatment are typically patients for whom the standard-of-care treatment is contraindicated, or, more broadly, who are ineligible for said treatment. Patients for whom there is a high risk of intolerance to the standard-of-care treatment thus have an unfavorable benefit/risk ratio with respect to said treatment.

For example, according to recently published clinical recommendations for systemic therapy of head and neck cancer in the elderly, "fit patients" should primarily be considered for high-dose of cisplatin with curative intent, while treatment in those who are frail rather consists of palliative measures, such as palliative irradiation and/or palliative surgical interventions (e.g., tracheostomy, gastrostomy) [cf. *Petr Szturz* et al. *Cisplatin Eligibility Issues and Alternative Regimens in Locoregionally Advanced Head and Neck Cancer: Recommendations for Clinical Practice. Frontiers in Oncology, June 2019, Volume 9, Article 464*], but these "fit patients" *a priori* considered for high-dose of cisplatin may be considered as a particular high-risk population in the context of the present invention as further explained herein below.

Therefore, there is a critical need to provide these patients, unable to receive a standard-of-care treatment involving RT, or at high risk to undergo a standard-of-care treatment involving RT, with an adapted treatment, typically, with a treatment having curative intent with optimum benefit / risk ratio outcome.

SUMMARY

Herein described are nanoparticles and/or aggregates of nanoparticles for use in the treatment of cancer in a human patient unable/ineligible to undergo a standard-of-care treatment involving RT, or in a patient at high risk of intolerance to a standard-of-care treatment involving RT, wherein the nanoparticles and/or aggregates of nanoparticles comprise more than 30% by weight of at least one chemical element having an atomic number (Z) between 20 and 83, and wherein the treatment of cancer involves a step of administering the nanoparticles and/or aggregates of nanoparticles to said patient, and a step of exposing the patient who has been administered with the nanoparticles and/or aggregates of nanoparticles to a total dose of ionizing radiations that is equal to or less than 85%, preferably, equal to

or less than 80%, more preferably, equal to or less than 75%, even more preferably, equal to or less than 70%, of the total dose delivered in the standard-of-care treatment involving RT for said cancer.

In a particular example, the patient fulfils at least one of the following criteria:

a. is vulnerable or frail according to the comprehensive geriatric assessment (CGA),

b. has a high comorbidity index score as evaluated using the Adult Comorbidity Evaluation 27 (ACE-27) and the Charlson Comorbidity Index (CCI),

c. has grade 2 or more organ dysfunction based on the National Cancer Institute Common Toxicity Criteria (NCI CTC),

d. has poor functional status as measured as an ECOG performance status of 2 or more, or as an equivalent Karnofski performance status,

e. is exposed to more than 4 distinct prescribed drugs,

f. is elderly and evaluated as "fit", according to part or full components evaluation of CGA, but presents cumulative exposure to risk factors for being intolerant to treatment,

g. has a locally advanced tumor observed at clinical staging,

In a particular example, the patient has an inoperable stage IIIA or IIIB Non-Small Cell Lung Carcinoma (NSCLC) tumor at clinical staging.

In a particular example, the cancer is selected from a skin cancer, a central nervous system cancer, a head and neck cancer, a lung cancer, a breast cancer, a gastrointestinal cancer, a male genitourinary cancer, a gynecologic cancer, an adrenal and/or retroperitoneal cancer, a sarcoma of bone and soft tissue, or a pediatric cancer.

In a particular example, the patient has a locally advanced stage III or IV squamous cell carcinoma of the head and neck (SCCHN) at clinical staging and receives a total dose of radiation of equal to or less than 59.5 Gy, preferably, equal to or less than 56 Gy, more preferably, equal to or less than 52.5 Gy, even more preferably, equal to or less than 50 Gy, delivered either as a stand-alone treatment, or in combination with chemotherapy or any other relevant systemic modality.

In a particular aspect, there is provided use of nanoparticles and/or aggregates of nanoparticles in the manufacture of a medicament for the treatment of locally advanced stage III or IV squamous cell carcinoma of the head and neck (SCCHN) in a human patient ineligible to undergo a standard-of-care treatment involving a radiotherapy (RT) dose of 70 Gy because said standard-of-care treatment is contraindicated for said patient, wherein the nanoparticles and/or aggregates of nanoparticles comprise more than 30% by weight of at least one chemical element having an atomic number (Z) between 20 and 83, wherein the medicament reduces the total dose of ionizing radiation of equal to or less than 59.5 Gy, delivered as a stand-alone treatment or in combination with chemotherapy or any other relevant systemic modality.

In a particular example, the patient has a stage IIIA or stage IIIB non-small cell Lung Carcinoma (NSCLC) tumor evaluated as inoperable at clinical staging, and receives a total dose of radiation equal to or less than 56.1 Gy, preferably, equal to or less than 52.8 Gy or 51 Gy, more preferably, equal to or less than 50 Gy, even more preferably, equal to or less than 49.1 Gy, 48 Gy or 42 Gy, delivered as a stand-alone treatment or in combination with chemotherapy or any other relevant systemic modality.

In a particular example, the patient has an operable locally advanced esophageal cancer tumor, preferably a squamous cell esophageal cancer tumor, and receives a preoperative total dose of radiation equal to or less than 35.2 Gy, preferably, equal to or less than 33.1 Gy or 31.1 Gy, more preferably, equal to or less

than 30 Gy, even more preferably, equal to or less than 29 Gy, delivered as a stand-alone treatment or in combination with chemotherapy or any other relevant systemic modality.

In a particular example, the patient has glioblastoma and receives a total dose of radiation equal to or less than 51 Gy, preferably, equal to or less than 48 Gy, more preferably, equal to or less than 42 Gy, delivered as a stand-alone treatment or in combination with chemotherapy or any other relevant systemic modality.

Herein further described are a pharmaceutical composition comprising nanoparticles and/or aggregates of such nanoparticles and a pharmaceutically acceptable carrier or support, as well as uses thereof in a human patient unable/ineligible to undergo a standard-of-care treatment involving RT, or in human patient at high risk to intolerance to a standard-of-care treatment involving RT.

DETAILED DESCRIPTION

The terms "**cancer staging**" refer to the evaluation of the extent or stage of cancer typically at the time of diagnosis. Several staging systems exist. In the "TNM" staging system, (i) the "T" refers to the size or contiguous extension of the primary tumor; (ii) the "N" refers to the absence, or presence and extent of cancer in the regional draining lymph nodes; and (iii) the "M" refers to whether the cancer has metastasized or not. The TNM system helps describe cancer in greater detail. This system classifies the extent of disease based mostly on anatomic information on the extent of the primary tumor, on the presence or absence of regional lymph nodes, and on the presence or absence of distant metastases. Still, for many cancers, the TNM combinations are grouped into five less-detailed stages, starting from stage 0 (corresponding, typically, to the presence of abnormal cells) up to stage 4 (or stage IV) (corresponding to a situation where, typically, the cancer has spread to distant parts of the body).

The terms **"clinical stage"** or **"clinical staging"** refer to the extent of disease, as defined by diagnostic study and includes any information obtained about the extent of cancer before initiation of definitive treatment. The nomenclature for clinical staging is "cT", "cN" and "cM", and the anatomic stage/prognostic groups based on cTNM are termed the clinical stage groups. Clinical staging incorporates information obtained from symptoms; physical examination; endoscopic examinations; imaging studies of the tumor, regional lymph nodes, and metastases; biopsies of the primary tumor; and surgical exploration without resection. When "T" is classified only clinically ("cT"), information from biopsy of single or sentinel lymph nodes may be included in clinical node staging ("cN"). On occasion, information obtained at the time of surgery may be classified as "clinical", such as, for example, when

CLAIMS

1. Use of nanoparticles and/or aggregates of nanoparticles in the manufacture of a medicament for the treatment of locally advanced stage III or IV squamous cell carcinoma of the head and neck (SCCHN) in a human patient ineligible to undergo a standard-of-care treatment involving a radiotherapy (RT) dose of 70 Gy because said standard-of-care treatment is contraindicated for said patient, wherein the nanoparticles and/or aggregates of nanoparticles comprise more than 30% by weight of at least one chemical element having an atomic number (Z) between 20 and 83, wherein the medicament reduces the total dose of ionizing radiation of equal to or less than 59.5 Gy, delivered as a stand-alone treatment or in combination with chemotherapy or any other relevant systemic modality.

2. Use according to claim 1, wherein the patient fulfils at least one of the following criteria:
   a. is vulnerable or frail according to the comprehensive geriatric assessment (CGA),
   b. has a high comorbidity index score as evaluated using the Adult Comorbidity Evaluation 27 (ACE-27) and the Charlson Comorbidity Index (CCI),
   c. has grade 2 or more organ dysfunction based on the National Cancer Institute Common Toxicity Criteria (NCI CTC),
   d. has poor functional status as measured as an ECOG performance status of 2 or more, or as an equivalent Karnofski performance status,
   e. is exposed to more than 4 distinct prescribed drugs,
   f. is elderly and evaluated as “fit”, according to part or full components evaluation of CGA, but presents cumulative exposure to risk factors for being intolerant to treatment.

3. Use according to claim 1 or 2, wherein each nanoparticle comprises at least one chemical element selected from La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ir, Pt, Au and Bi.

4. Use according to any one of claims 1-3, wherein the nanoparticles are inorganic nanoparticles.

5. Use according to any one of claims 1-4, wherein each nanoparticle and/or aggregate of nanoparticles further comprises a biocompatible surface coating.

6. Use according to any one of claims 1-5, wherein the nanoparticles are selected from a HfO_2 nanoparticle, a Au nanoparticle, a ReO_2 nanoparticle and any mixture thereof.

7. Use according to any one of claims 1-6, wherein the ionizing radiation is selected from X-rays, gamma-rays, electrons and protons.

8. Use according to any one of claims 1-7, wherein the medicament is to be administered with at least one distinct therapeutic agent, either simultaneously or separately.

9. Use according to claim 8, wherein the at least one distinct therapeutic agent is an immunotherapeutic agent selected from a monoclonal antibody, a cytokine and a combination thereof.

10. Use according to claim 9, wherein the at least one distinct therapeutic agent is selected from a biological compound, a small molecule targeted therapeutic, a cytotoxic compound and a combination thereof.

11. Use according to any one of claims 1-10, wherein the medicament reduces the total dose of ionizing radiation of equal to or less than 56 Gy.

12. Use according to any one of claims 1-11, wherein the medicament reduces the total dose of ionizing radiation of equal to or less than 52.5 Gy.

13. Use according to any one of claims 1-12, wherein the medicament reduces the total dose of ionizing radiation of equal to or less than 50 Gy.