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DESCRIPTION

Description

[0001] This invention relates to a composition for use in an intravesical (i.e. inside the bladder) therapy for bladder cancer.

[0002] Bladder cancer is the ninth most common cancer diagnosis worldwide, with more than 330 000 new cases each year and more than 130 000 deaths per year. At any point in time, 2.7 million people have a history of urinary bladder cancer.

[0003] The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder (cystoscopy) and histological evaluation of the resected tissue. In general, cystoscopy is initially performed in the office, using flexible instruments. At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC).

[0004] If a bladder tumor has been detected during cystoscopy, the patient will undergo transurethral resection (TUR), i.e. a procedure where the bladder is visualized through the urethra and tumors and lesions are resected. In case of NMIBC, such a resection is to completely remove the tumor, in case of MIBC; such a resection is of a palliative nature. Apart from the resection of the tumor, the TUR is also carried out to enable a correct histological diagnosis of the resected tumor/tumor biopsies by a pathologist.

[0005] For patients with MIBC, the standard treatment for is radical cystectomy, i.e. removal of the bladder and adjacent organs, that is prostate and seminal vesicles in men, and uterus and adnexa in women. It also includes the dissection of regional lymph nodes. Cystectomy is also advocated in patients with NMIBC who are at high risk of progression, i.e. patients having multiple recurrent high-grade tumors or high-grade T1 tumors or high-grade tumors with concurrent carcinoma-in-situ (CIS). Further, cystectomy is advocated in patients with NMIBC who have received Bacillus Calmette-Guérin (BCG) immunotherapy but where such treatment has failed.

[0006] Although being the gold standard for MIBC treatment and advocated in patients with certain types of NMIBC, radical cystectomy only provides 5-year survival in about 50% of patients. In order to improve these unsatisfactory results, the use of neoadjuvant therapies has been explored since the 1980s.

[0007] Currently, neoadjuvant radiotherapy and neoadjuvant chemotherapy is used. With neoadjuvant radiotherapy, down staging of the cancer after radiotherapy takes about 4-6 weeks. However, a delay of surgery in patients with locally advanced bladder cancer beyond

90 days has shown to cause a significant increase in extravesical disease (81 vs 52%). Neoadjuvant radiotherapy is not recommended according to the current European guidelines on MIBC since no data exist to support that neoadjuvant radiotherapy for operable MIBC increases survival.

[0008] Neoadjuvant chemotherapy has many advantages including that chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low; that tolerability of chemotherapy is expected to be better before cystectomy rather than after; and that hypothetically patients with micrometastatic disease might respond to neoadjuvant therapy and reveal favorable pathological status determined mainly by negative lymph node status and negative surgical margins. Neoadjuvant cisplatin-containing chemotherapy has shown to significantly improve survival (5% absolute improvement in survival at 5 years). However, as stated above, delayed cystectomy may compromise the outcome in patients who are not sensitive to chemotherapy and generally, pre-operative anemia and neuropathy is more common in patients receiving neoadjuvant chemotherapy prior to cystectomy. The current European guidelines on MIBC state that "....neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical technique, and current chemotherapy combinations." Hence, there is room for improvement of neoadjuvant therapies for bladder cancer patients who are scheduled for a cystectomy , i.e. bladder cancer patients diagnosed with MIBC or NMIBC who are at high risk of progression, including multiple recurrent high-grade tumors or high-grade T1 tumors or high-grade tumors with concurrent carcinoma-in-situ (CIS).

[0009] For patients with NMIBC, the standard treatment is resection of the tumor by TUR. Instillation into the bladder of a patient of a composition comprising HAL or a pharmaceutically acceptable salt thereof and exposing the inside of said bladder to blue light may be used to improve visualization of bladder cancer during cystoscopy and/or TUR. As a standard procedure, cystoscopy and TUR are performed using white light. However, since the use of white light can lead to missing lesions that are present but not visible, photodynamic diagnosis (PDD) is often used in such procedures. PDD involves the administration of a photosensitizer or a precursor thereof (i.e. a "photosensitizing agent") to an area of interest. The photosensitizer or precursor thereof is taken up into the cells, where a precursor of a photosensitizer is converted into an active photosensitizer. Upon exposure of the area of interest to light of a suitable wavelength, the photosensitizer is excited and, upon relaxation to its ground state, fluorescence occurs.

[0010] Hexyl 5-ALA ester (hexaminolevulinate, HAL) and its salts are such photosensitizing agents. HAL preferably penetrates rapidly proliferating cells, e.g. tumor cells, where it is converted into porphyrins, which are photosensitizers and fluorescent compounds. Under subsequent blue-light illumination, the porphyrins emit red light and thus enable specific and accurate visualization of the tumor. Hexvix® (Photocure ASA, Norway), in the US and Canada marketed as Cysview® is a commercially available approved drug that comprises HAL and is used in PDD in cystoscopy and TUR procedures.

[0011] In patients with NMIBC, HAL-guided cystoscopy and TUR has increased detection of both papillary tumors and flat carcinoma-in-situ (CIS) lesions, the latter of which are difficult to detect with white light alone. HAL-guided TUR of bladder cancer in patients with NMIBC has further reduced the rate of residual tumor after such procedures and has led to superior recurrence free survival (RFS) rates and prolonged RFS intervals compared to white light TUR alone (see Rink M, et al. Eur Urol 4(64), 2013, 624). Existing European guidelines on NMIBC and several expert groups consensus statements recommend the use of HAL-guided TUR in various settings of management of NMIBC and some even recommend its use in all NMIBC patients at initial TUR (see Witjes JA, et al., Eur Urol 1(66), 2014, 863).

[0012] Although a TaT1 tumor can be completely resected by HAL-guided TUR, and HAL-guided TUR favorably affects recurrence rate, these tumors may recur and progress to muscle-invasive bladder cancer in a limited number of cases. It is therefore necessary to consider adjuvant therapy, i.e. adjuvant chemotherapy or adjuvant chemotherapy and adjuvant immunotherapy, in all patients. The choice of therapy may be considered differently according to what risk is acceptable for the individual patient. Usually, a patient will receive one immediate, post-TUR instillation of chemotherapy into the bladder. The need for further adjuvant intravesical therapy depends on the patients' prognosis. In patients with a low risk of tumor recurrence, a single immediate instillation reduces the risk of recurrence and is considered as the standard treatment, i.e. no further treatment is given in these patients before recurrence. For other patients, however, a single immediate instillation remains an incomplete treatment because the likelihood of recurrence and/or progression is considerable. There is no single chemotherapy drug that is superior with regard to efficacy; mitomycin C, epirubicin, and doxorubicin have all shown a beneficial effect. However, mitomycin C (MMC) is often the drug of choice.

[0013] According to EAU guidelines for the treatment of NMIBC, in patients with TaT1 tumors at intermediate or high risk of recurrence and intermediate or high risk of progression, one immediate instillation of chemotherapy should be followed by a minimum one year of Bacillus Calmette-Guérin (BCG) immunotherapy, or by further instillations of chemotherapy. In patients with bladder CIS, intravesical BCG for at least one year is indicated.

[0014] Assuming that maintenance therapy with BGC is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. As a result of the more pronounced side effects of BCG compared to intravescial chemotherapy, there is still a reluctance about the use of BCG. Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis and allergic reactions have compromised its use. In addition, treatment failure of BCG is not uncommon.

[0015] In view of the above, there is a high need of new types of adjuvant and neoadjuvant therapy for the management of bladder cancer.

[0016] Such a new therapy includes the use of anti-PD-LI antibodies. Anti-PD-LI is an investigational monoclonal antibody designed to interfere with a protein called PD-L1. Anti-PD-LI targets PD-L1 expressed on cancer cells and tumor-infiltrating immune cells, preventing it

from binding to PD-1 and B7.1 on the surface of T cells. By inhibiting PD-L1, anti-PD-LI may enable the activation of T cells, restoring their ability to effectively detect and attack cancer cells, e.g. bladder cancer cells. As used herein, the term "anti-PD-L1 antibodies" refers to antibodies which inhibit PD-L1.

[0017] Another new therapy includes the use of anti-PD-I antibodies, preferably anti-PD-I antibodies. Anti-PD-I is an investigational monoclonal antibody that binds to the PD-L1 (programmed death-ligand 1) protein, which is present at high levels in many cancer types, e.g. bladder cancer. By competitively blocking the interaction with PD-1 receptors, it is believed that anti-PD-I thereby restores anti-cancer T-cell responses. As used herein, the term "anti-PD-1 antibodies" refers to antibodies which inhibit PD-1.

[0018] Thus, anti-PD-LI antibodies and anti-PD-1 antibodies target different components of the same interaction mechanism between immune cells (specifically killer T cells) and cancer cells, but have a similar therapeutic effect: anti-PD-L1 antibodies target PD-L1 (programmed death ligand-1) expressed on cancer cells while anti-PD-1 antibodies target the other half of this mechanism, PD-1 (programmed death receptor-1), which is expressed on killer T cells.

[0019] Both anti-PD-LI antibodies and anti-PD-I antibodies are mainly for parenteral or intravenous administration. Such administrations may lead to side effects due to systemic distribution of the drug.

[0020] Sundararajan et al., Future Oncology, Vol. 11, No. 16, 1 August 2015, pages 2299-2306 disclose the use of anti-PD-1 or anti-PD-L1 antibodies for the treatment of bladder cancer. The antibodies are not administered intravesically.

[0021] Saylor, "Product Preview: Agreement reached for phase III clinical trial of bladder Ca agent", Urology Times, 1 September 2015, announces the phase III clinical trial of intravesical apaziquone for the treatment of patients with NMBC.

[0022] Jokish, Indian Journal of Urology, 2015, Oct-Dec 31(4): 304-311 reviews current treatments for bladder cancer. The discussion relating to the use of immune checkpoint inhibitors is limited to treatment of metastatic stages of bladder cancer using MPDL3280A (atezolizumab) which targets PD-L1. It does not disclose instillation of any anti-PD-L1 and/or anti-PD-1 immunotherapy into the bladder to treat bladder cancer.

[0023] Hurwitz et al., "The effect of BCG intravesical therapy and recurrence on PDL1 expression in non-invasive bladder cancers, 2015 ASCO Annual Meeting, Abstracts", 29 May 2015, examines the expression of PD-L1 in non-invasive bladder cancers and the extent to which its expression may be affected by treatment with intravesical BCG.

[0024] We now suggest that a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies and hexyl 5-ALA ester or a pharmaceutically acceptable salt thereof is used for intravescial therapy in patients with bladder cancer.

[0025] The scope of the invention is defined by the claims. Any reference herein to methods of therapy refer to the compositions for use in a method of therapy according to the present invention. Methods of medical treatment do not form part of the invention.

[0026] In a first aspect, the invention provides a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies and hexyl 5-ALA ester or a pharmaceutically acceptable salt thereof for use in a method of therapy for bladder cancer, wherein said composition is instilled into the bladder of a patient with bladder cancer and wherein after instillation of said composition into the bladder of said patient, the inside of the bladder is exposed to light.

[0027] The term "anti-PD-LI antibodies and/or anti-PD-I antibodies" means that the composition for use in the invention either comprises anti-PD-LI antibodies or comprises anti-PD-I antibodies or comprises both anti-PD-LI antibodies and anti-PD-I antibodies.

[0028] Preferred anti-PD-LI antibodies are those by Roche, preferably MPDL3280A. Said preferred anti-PD-LI antibodies are described in WO 2010/077634, WO 2013/019906 and WO 2013/181452.

[0029] Preferred anti-PD-I antibodies are those by Merck, preferably pembrolizumab (Keytruda). Such preferred anti-PD-I antibodies are described in WO2008/156712, WO 2009/114335 and WO 2013/079174.

[0030] Other preferred anti-PD-I antibodies are those by Bristol-Myers Squibb, preferably nivolumab (Opdivo). Such preferred anti-PD-I antibodies are described in WO 2004/004771.

[0031] The bladder cancer in the context of the invention is either muscular invasive bladder cancer (MIBC) or non-muscular invasive bladder cancer (NMIBC).

[0032] For patients who are scheduled for a cystectomy, i.e. who either have MIBC or NMIBC with a high risk of progression, including multiple recurrent high-grade tumors or high-grade T1 tumors or high-grade tumors with concurrent carcinoma-in-situ (CIS), the therapy according to the invention is a neoadjuvant therapy. The term "neoadjuvant therapy" means the administration of a therapeutic agent before/prior to the main treatment for the disease. In the context of the invention, the main treatment for such patients is cystectomy and the disease is MIBC or NMIBC with a high risk of progression, including multiple recurrent high-grade tumors or high-grade T1 tumors or high-grade tumors with concurrent carcinoma-in-situ (CIS).

[0033] In one embodiment, the invention provides a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies and hexyl 5-ALA ester or a pharmaceutically acceptable salt thereof for use in a method of neoadjuvant therapy for bladder cancer, wherein said composition is instilled into the bladder of a bladder cancer patient who is scheduled for a cystectomy and wherein after instillation of said composition into the bladder of said patient, the inside of the bladder is exposed to light.

[0034] For patients with NMIBC where cystectomy is not advocated, e.g. who have TaT1 tumors with low risk of recurrence and progression, or TaT1 tumors with intermediate or high risk of recurrence and intermediate risk of progression or CIS, the therapy according to the invention is an adjuvant therapy. The term "adjuvant therapy" means the administration of a therapeutic agent in addition to the main treatment for the disease. In the context of the invention, the main treatment for such patients is TUR and the disease is NMIBC where cystectomy is not advocated.

[0035] In a further embodiment, the invention provides a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies and hexyl 5-ALA ester or a pharmaceutically acceptable salt thereof for use in a method of adjuvant therapy for bladder cancer, wherein said composition is instilled into the bladder of a bladder cancer patient who undergoes TUR and wherein after instillation of said composition into the bladder of said patient, the inside of the bladder is exposed to light.

[0036] The adjuvant therapy according to the invention can be carried out prior, simultaneously or after said TUR.

[0037] The composition for use in the invention may comprise pharmaceutically acceptable carriers, excipients, or stabilizers. The composition for use in the invention is preferably a semi-solid composition or a liquid composition. The term "semi-solid" denotes a physical state which is neither solid nor liquid. Semi-solids (or quasi-solids) are similar to a solid in some respects, e.g. a semi-solid can support its own weight and hold its shape but also shares some properties of liquids, such as shape conformity to something applying pressure to it, or the ability to flow under pressure. Semi-solids are characterized by a three-dimensional structure that is sufficient to impart solid-like character to the undisturbed system but that is easily broken down and realigned under an applied force. Semi-solids have a rigidity and viscosity intermediate between a solid and a liquid. Preferred semi-solid compositions are foams, gels and lotions, preferably low viscosity gels and lotions. However, liquid compositions are preferred, especially liquid compositions that are solutions or suspensions of anti-PD-LI antibodies and/or anti-PD-I antibodies, i.e. more preferably comprising anti-PD-LI antibodies and/or anti-PD-I antibodies in a liquid carrier. Preferred liquid carriers are water or aqueous solutions, most preferably aqueous buffers.

[0038] If the composition for use in the invention is a liquid composition comprising water, the pH of said composition is preferably in the range of 4.5 to 7.5.

[0039] The composition for use in the invention preferably comprises a therapeutically effective amount of anti-PD-LI antibodies and/or anti-PD-I antibodies. Such therapeutically effective amount can be administered in one or more instillations into the bladder. For purposes of this invention, a therapeutically effective amount of anti-PD-LI antibodies and/or anti-PD-I antibodies is an amount sufficient to accomplish therapeutic treatment together with at least the main treatment, i.e. cystectomy or TUR. Other neoadjuvant or adjuvant treatments may be carried out together with the therapy of the invention, e.g. neoadjuvant radiotherapy,

(neo)adjuvant chemotherapy or (neo)adjuvant immunotherapy.

[0040] The amount of the composition for use in the invention which is instilled into the bladder may vary according to the bladder volume and size of the bladder of the patient. In general, a volume of about 50 ml of the composition is instilled.

[0041] The composition for use in the invention is instilled preferably into the empty bladder through a catheter and is left in the bladder from about 20 minutes to about 3 hours, more preferably from about 30 minutes to about 2 hours, most preferably no less than 1 hour.

[0042] The composition of the invention comprises hexyl 5-ALA ester (HAL) or a pharmaceutically acceptable salt thereof.

[0043] As mentioned above, HAL-guided TUR in patients with NMIBC has led to superior recurrence free survival (RFS) rates and prolonged RFS intervals compared to white light TUR alone. Also, HAL-guided TUR in patients with MIBC seem to have an impact on recurrence free survival: in 268 consecutive patients who underwent cystectomy for bladder cancer it was retrospectively investigated whether patients prior to the cystectomy had undergone HAL-guided TUR or whether TUR was carried out with white light alone. Kaplan-Meier analysis was used to estimate recurrence-free survival (RFS) and overall survival (OS). The 3-year RFS was 69.8% in patients with HAL-guided TUR and 58.2% in patients with white light TUR alone. The 3-year OS was 65.0% in patients with HAL-guided TUR and 56.6%. These results indicate that HAL-guided TUR is associated with improved RFS after cystectomy in patients with MIBC (see G. Gakis et al., Urology Vol. 82, Issue 3, Supplement, Unmoderated Posters, UP.046).

[0044] The term "5-ALA" denotes 5-aminolevulinic acid, i.e. 5-amino-4-oxo-pentanoic acid.

[0045] The term "hexyl 5-ALA ester" (HAL) denotes n-hexyl aminolevulinate, i.e. n-hexyl 5-amino-4-oxo-pentanoate.

[0046] The term "pharmaceutically acceptable salt" denotes a salt that is suitable for use in the dry pharmaceutical product and which fulfils the requirements related to for instance safety, bioavailability and tolerability (see for instance P. H. Stahl et al. (eds.) Handbook of Pharmaceutical Salts, Publisher Helvetica Chimica Acta, Zurich, 2002).

[0047] The synthesis of hexyl 5-ALA ester is known in the art and may be prepared as described in e.g. WO 96/28412. Briefly, hexyl 5-ALA ester may be prepared by reaction of 5-ALA with hexanol in the presence of a catalyst, e.g. an acid. Further, hexyl 5-ALA ester hydrochloride is commercially available, e.g. in the form of Hexvix® (Photocure ASA and Ipsen Pharma SA) or Cysview® (Photocure Inc.).

[0048] The hexyl 5-ALA ester for use in embodiments of the invention is preferably in the form of a pharmaceutically acceptable salt. Such salts are preferably acid addition salts with

pharmaceutically acceptable organic or inorganic acids. Suitable acids include, for example, hydrochloric, nitric, hydrobromic, phosphoric, sulfuric, sulfonic acid and sulfonic acid derivatives, the salts of ALA-esters and the latter acids are described in WO 2005/092838 to Photocure ASA. A preferred acid is hydrochloride acid, HCl. Synthetic procedures for salt formation are conventional in the art and are for instance described in WO 2005/092838.

[0049] The concentration of HAL in the composition for use in the invention is conveniently in the range of 0.1 to 5 % by weight of the total weight of the composition or the equivalent concentration of a pharmaceutically acceptable salt of HAL, preferably 0.15 to 3.5%, and most preferably 0.17%. In a most preferred embodiment, the hydrochloride salt of HAL is used in the composition at a concentration of 0.2%.

[0050] In a preferred embodiment, the composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof for use in the invention is a liquid composition. Preferred liquid carriers are water or aqueous solutions, most preferably aqueous buffers.

[0051] In a preferred embodiment, the liquid carrier is an aqueous phosphate buffer, preferably an aqueous phosphate buffer which comprises disodium phosphate dehydrate, potassium dihydrogen phosphate, sodium chloride, hydrochloric acid, sodium hydroxide and water. If the composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof for use in the invention is a composition comprising water, said composition has a pH in the range of 4.5 to 7.5, more preferably in the range of 5.7 and 7.2.

[0052] The amount of the composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof, which is instilled into the bladder, may vary according to the bladder volume and size of the bladder of the patient. In general, a volume of about 50 ml of the composition is instilled.

[0053] The composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof for use in the invention is instilled preferably into the empty bladder through a catheter and is left in the bladder from about 20 minutes to about 3 hours, more preferably from about 30 minutes to about 2 hours, most preferably no less than 1 hour. If the patient cannot retain the composition for 1 hour, at least 1 hour should be allowed to pass from the instillation of the composition into the bladder to the start of exposing the inside of the bladder to light.

[0054] For exposing the inside of the bladder to light, any wavelength of light which is suitable to excite the hexyl 5-ALA ester may be used. Preferred is white light, i.e. visible light with wavelengths of from about 350 to 700 nm and/or blue light, i.e. wavelengths of from about 360 nm to about 450 nm and/or red light, i.e. wavelengths of from about 600 to 670 nm. The term and/or means that e.g. the inside of the bladder is exposed to either white or blue light or to white light and blue light, subsequently and not at the same time. Especially preferred is white

light and/or blue light, more preferred white light followed by blue light.

[0055] For exposing the inside of the bladder to light, approved cystoscopic light sources are preferred which allow both for white light and blue light irradiation of the inside of the bladder. Such cystoscopes are commercially available, e.g. from Karl Storz (Photodynamic Diagnostic D-Light C (PDD) System), Olympus or Richard Wolf). For red light irradiation, such equipment may be modified with the suitable filters. Such cystoscopic light sources may be rigid or flexible.

[0056] The light dose given during irradiation of the inside of the bladder with use of white and blue light may vary but is preferably 0.01 to 100 J/cm2, more preferably 0.03 - 40 J/cm^2 and most preferably 0.1 to 3 J/cm^2. For a cystoscopic light source with a output in the range of 47 - 82 mW such a light dose is provided in about 10 to 30 minutes (calculated based on a 300 cm^2 surface area for a human bladder).

[0057] The method of therapy according to the invention may be used as a neoadjuvant therapy for bladder cancer patients who are scheduled for a cystectomy.

[0058] In one embodiment, the invention provides a composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) hexyl 5-ALA ester (HAL) or a pharmaceutically acceptable salt thereof for use in a method of neoadjuvant therapy for bladder cancer, said therapy comprising (i) instillation of said composition into the bladder of a patient with bladder cancer who is scheduled for a cystectomy; and (ii) exposing the inside of said bladder to light.

[0059] The time between the method of neoadjuvant therapy of the invention, i.e. instillation into the bladder of a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies or a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof and exposing the inside of said bladder to light and the cystectomy may vary but is preferably zero to 6 weeks, e.g. zero to 1, 2, 3, 4, 5 or 6 weeks and more preferably zero to 3 weeks, e.g. 1 or 2 weeks. "Zero" means that the cystectomy is carried out directly after the light irradiation is finalized. This has the advantage that the patient is only anaesthetized once.

[0060] As mentioned earlier, bladder cancer patients who are scheduled for a cystectomy are those diagnosed with MIBC or NMIBC with a high risk of progression, including multiple recurrent high-grade tumors or high-grade T1 tumors or high-grade tumors with concurrent carcinoma-in-situ (CIS).

[0061] The neoadjuvant therapy of the invention may be carried out once or repeatedly prior to the cystectomy, i.e. carried out two or more times, e.g. 3, 4, 5 or 6 times, with a period between the treatments of e.g. 4 days to 4 weeks, e.g. 1, 2 or 3 weeks.

[0062] The neoadjuvant therapy of the invention may be carried out prior, simultaneously or after other neoadjuvant therapies, including neoadjuvant radiotherapy, neoadjuvant

chemotherapy (intravescial instillation or systemic administration) with e.g. cisplatin, methotrexate, vinblastine, valurubicin, adriamycin, mitomycin C or combinations thereof and neoadjuvant immunotherapy (intravescial instillation or systemic administration) with e.g. BCG.

[0063] After cystectomy, the patient may receive systemic adjuvant chemotherapy with e.g. cisplatin, methotrexate, vinblastine, adriamycin, gemcitabine, doxorubicin, epirubicin, cyclophosphamide or combinations thereof. Alternatively or in addition thereto, the patient may receive systemic adjuvant immunotherapy with e.g. anti-PD-LI antibodies and/or anti-PD-I antibodies.

[0064] The method of therapy according to the invention may be used as an adjuvant therapy for bladder cancer patients who undergo TUR, i.e. patients who are diagnosed with NMIBC.

[0065] In a further embodiment, the invention provides a composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) hexyl 5-ALA ester (HAL) or a pharmaceutically acceptable salt thereof for use in a method of adjuvant therapy for bladder cancer, said therapy comprising (i) instillation of said composition into the bladder of a patient with bladder cancer who undergoes TUR; and (ii) exposing the inside of said bladder to light.

[0066] The time between said TUR and the adjuvant therapy of the invention, i.e. instillation into the bladder of a composition comprising anti-PD-LI antibodies and/or anti-PD-I antibodies is preferably zero to 6 weeks, e.g. zero to 1, 2, 3, 4, 5 or 6 weeks and more preferably zero to 3 weeks, e.g. 1 or 2 weeks. "Zero" means that the adjuvant therapy according to the invention is carried out directly after said TUR.

[0067] If the adjuvant therapy according to the invention comprises the instillation into the bladder of a composition comprising a) anti-PD-LI antibodies and/or anti-PD-I antibodies and b) HAL or a pharmaceutically acceptable salt thereof and exposing the inside of said bladder to light, the TUR may be carried out simultaneously with said therapy, since the use of HAL enables detection and thus accurate resection of the tumor.

[0068] The adjuvant therapy of the invention may be carried out prior, simultaneously or after other neoadjuvant or adjuvant therapies, including (neo)adjuvant radiotherapy, (neo)adjuvant chemotherapy (intravescial instillation or systemic administration) with e.g. cisplatin, methotrexate, vinblastine, valurubicin, adriamycin, mitomycin C or combinations thereof and (neo)adjuvant immunotherapy (intravescial instillation or systemic administration) with e.g. BCG or anti-PD-LI antibodies and/or anti-PD-I antibodies.

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- **JOKISH**Indian Journal of Urology, 2015, vol. 31, 4304-311 [0022]
- **HURWITZ et al.**The effect of BCG intravesical therapy and recurrence on PDL1 expression in non-invasive bladder cancers2015 ASCO Annual Meeting, Abstracts, 2015, [0023]
- **G. GAKIS et al.**Urology, vol. 82, 3 [0043]
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Patentkrav

1. Sammensætning omfattende anti-PD-L1-antistoffer, som inhiberer PD-L1- og/eller anti-PD-1-antistoffer, som inhiberer PD-1 og hexyl-5-ALA-ester eller et farmaceutisk acceptabelt salt deraf til anvendelse i en fremgangsmåde til terapi af blærekræft, hvor sammensætningen indpodes i blæren på en patient med blærekræft, og hvor det indre af blæren efter indpodningen af sammensætningen i blæren på patienten udsættes for lys.

2. Sammensætningen til anvendelse ifølge krav 1, hvor sammensætningen omfatter enten anti-PD-L1-antistofferne eller anti-PD-1-antistofferne, eller hvor sammensætningen omfatter anti-PD-L1-antistofferne og anti-PD-1-antistofferne.

3. Sammensætningen til anvendelse ifølge krav 1 eller krav 2, hvor anti-PD-L1-antistoffet er MPDL3280A, og/eller hvor anti-PD-1-antistoffet er pembrolizumab eller nivolumab.

4. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor sammensætningen omfatter en terapeutisk effektiv mængde af anti-PD-L1-antistofferne og/eller anti-PD-1-antistofferne.

5. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor sammensætningen er en halvfast sammensætning eller en flydende sammensætning, fortrinsvis en sammensætning omfattende anti-PD-L1-antistofferne og/eller anti-PD-1-antistofferne i en flydende bærer, f.eks. i vand eller vandig opløsning, fortrinsvis en vandig buffer.

6. Sammensætningen til anvendelse ifølge krav 5, hvor sammensætningen er en flydende sammensætning omfattende vand, pH-værdien af sammensætningen er i området fra 4,5 til 7,5.

7. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor sammensætningen indpodes i blæren gennem et kateter og efterlades i blæren fra 20 minutter til 3 timer.

8. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor koncentrationen af hexyl-5-ALA-ester i sammensætningen er i området fra 0,1 til 5 vægt-% af den samlede vægt af sammensætningen eller den ækvivalente koncentration af et farmaceutisk acceptabelt salt af HAL.

9. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor sammensætningen er en flydende sammensætning opnået ved rekonstitution af frysetørrede a) anti-PD-L1-antistoffer, som inhiberer PD-L1- og/eller anti-PD-1-antistoffer, som inhiberer PD-1 og b) frysetørret hexyl-5-ALA-ester eller et farmaceutisk acceptabelt salt deraf i en flydende bærer, fortrinsvis i vand eller en vandig opløsning, mest fortrinsvis i en vandig buffer.

10. Sammensætningen til anvendelse ifølge et hvilket som helst af de foregående krav, hvor det indre af blæren udsættes for hvidt lys og/eller blåt lys og/eller rødt lys, fortrinsvis hvor det indre af blæren udsættes for hvidt lys efterfulgt af blåt lys.

11. Sammensætningen til anvendelse ifølge et hvilket som helst af kravene 1 til 10, hvor sammensætningen er til anvendelse i en fremgangsmåde til neoadjuverende terapi til blærekræftpatienter, som er planlagt til en cystektomi.

12. Sammensætningen til anvendelse ifølge krav 11, hvor tiden mellem udførelse af fremgangsmåden til neoadjuverende terapi og cystektomien er nul til 6 uger.

13. Sammensætningen til anvendelse ifølge et hvilket som helst af kravene 1 til 10, hvor sammensætningen er til anvendelse i en fremgangsmåde til adjuverende terapi til blærekræftpatienter, der gennemgår transurethral resektion (TUR), fortrinsvis hvor tiden mellem udførelse af fremgangsmåden til adjuverende terapi og TUR'en er nul til 6 uger.

14. Sammensætningen til anvendelse ifølge krav 13, hvor fremgangsmåden til adjuverende terapi og TUR'en udføres samtidigt.