lower doses achieve effects, chemotherapeutic agents that reach normal cells decrease, and the maximum tolerated doses increase.

[0005]

One approach to ADC is a radioimmunoconjugate. In radioimmunoconjugates, radionuclides are used instead of payloads.

[0006]

For example, Non Patent Literatures 1 and 2 describe $^{225}$Ac-labeled trastuzumab in which trastuzumab is randomly labeled with $^{225}$Ac by using 1,4,7,10-tetraazacyclododecane-1,4,7,10 tetraacetic acid (DOTA) as a chelating agent and reacting the isothiocyanate group introduced into DOTA with the terminal amino group of trastuzumab.

[0007]

In addition, Patent Literature 1 describes $^{225}$Ac-labeled trastuzumab and $^{225}$Ac-labeled Pertuzumab, in which trastuzumab and pertuzumab are ~~is~~ randomly labeled with $^{225}$Ac, as anti-HER2 antibodies which are obtained by randomly modifying trastuzumab and pertuzumab with an azide group, and subjecting them to a click reaction with DOTAGA-DBCO labeled with Ac-225.

[0008]

In addition, radioimmunoconjugates using radionuclides that emit gamma-ray and positron as radionuclides can be utilized for nuclear medicine examinations. Patent Literature 2 describes a conjugate of a peptide that site-specifically modifies the Fc region of an antibody and an anti-HER2 antibody. In addition, Patent Literature 3 describes that DTPA was introduced into this peptide to modify trastuzumab and trastuzumab was labeled with In-111 to obtain $^{111}$In-labeled trastuzumab, and that DFO was introduced into the peptide to modify trastuzumab and trastuzumab was labeled with Zr-89 to obtain $^{89}$Zr-labeled trastuzumab.

[Citation List]

[Patent Literature]

[0009]

[PTL 1]

WO2019/125982

[PTL 2]

WO2016/186206

[PTL 3]

WO2017/217347

[Non Patent Literature]

[0010]

[NPL 1]

Cancer Res.2003 Aug 15; 63(16):5084-90

[NPL 2]

Clin Cancer Res.2004 Jul 1; 10(13):4489-97

[Summary of Invention]

~~[Technical Problem]~~

[0011]

However, it has been clarified from the findings of the present inventors that a radioconjugate of the anti-HER2 antibody, which forms a thiourea bond through the reaction between DOTA into which an isothiocyanate group has been introduced and an amino group, has problems such as low stability.

[0012]

Patent Literature 1 does not describe site-specific modification of anti-HER2 antibody with peptides. In addition, it does not disclose or suggest the problem of anti-HER2 antibody that forms a thiourea bond.

~~[Solution to Problem]~~

[0013]

One embodiment of the present invention is a conjugate of an anti-HER2 antibody site-specifically modified with a peptide and a chelating agent, wherein the chelating agent is chelated with a metal radionuclide, the peptide and the chelating agent are linked by a linker (L), and the linker (L) does not contain

a thiourea bond.

[0014]

Another embodiment of the present invention is a radiopharmaceutical containing the above-mentioned conjugate as an active ingredient.

[0015]

In addition, another embodiment of the present invention is a radiopharmaceutical containing a conjugate of a chelating agent chelated with a metal radionuclide and an anti-HER2 antibody as active ingredients, wherein the linkage between the anti-HER2 antibody and the chelating agent does not contain a thiourea bond, and the conjugate has a radiochemical purity of not less than 90% when stored at room temperature for 7 days.

[0016]

The "linkage" in the present invention means both direct connection and indirect connection, unless otherwise specified.

~~[Advantageous Effects of Invention]~~

[0017]

According to the present invention, a radioconjugate of an anti-HER2 antibody is provided which has stability improved more than conventional conjugates without impairing the efficacy.

[Brief Description of Drawings]

[0018]

[Fig. 1]

A graph showing changes in tumor volume over time in tumor-bearing mice of a radioconjugate (Example 1) group, a radioconjugate (Comparative Example 1) group, an antibody control group, and a vehicle group. The vertical axis indicates relative values when the tumor volume at the time of administration of each medicament is set to 1, and the horizontal axis indicates the number of days elapsed since administration of each medicament. The graph represents the mean±standard deviation of tumor volume in each group, "*" is

N,N',N"-triacetic acid), H6phospa (N,N'-(methylenephosphonate)-N,N'-[6-(methoxycarbonyl)pyridin-2-yl]-methyl-1,2-diaminoethane), HP-D03A (Hydroxypropyltetraazacyclododecanetriacetic acid), and porphyrin. A compound represented by the following formula (A) is preferred.

[0029]

(A)




[0030]

In the formula (A), $R_{11}$, $R_{12}$, $R_{13}$ and $R_{14}$ are each independently a group consisting of $-(CH_2)_pCOOH$, $-(CH_2)_pC_5H_4N$, $-(CH_2)_pPO_3H_2$, $-(CH_2)_pCONH_2$ or $-(CHCOOH)(CH_2)_pCOOH$, $R_{15}$ is a hydrogen atom, and p is an integer of not less than 0 and not more than 3.

[0031]

The compound represented by the formula (A) is preferably a compound containing a structure derived from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), or a derivative thereof. Specifically, the compound can contain, in its structure, a structure derived from one chelating agent selected from DOTA (1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTMA ((1R,4R,7R,10R)-α,α',α",α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTAM (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane), DOTA-GA (α-(2-Carboxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTP (((1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(methylene))tetraphosphonicacid), DOTMP

radioconjugate of the present invention, some groups in the compound of the aforementioned chelating agent may be substituted by groups that form covalent bonds with the linker (L). For example, when the chelating agent used in the present invention is a compound represented by the formula (A), $R_{12}$ or $R_{15}$ may be substituted by a group that forms a covalent bond with the linker (L). Preferably, when $R_{12}$ is substituted by a group that forms a covalent bond with the linker (L), $R_{15}$ is a hydrogen atom, when $R_{12}$ is a group consisting of $-(CH_2)_pCOOH$, $-(CH_2)_pC_5H_5N$, $-(CH_2)_pPO_3H_2$, $-(CH_2)_pCONH_2$, or $-(CHCOOH)(CH_2)_pCOOH$, $R_{15}$ is substituted by a group that forms a covalent bond with the linker (L).

[0034]

The covalent bond between the chelating agent and the linker (L) only needs to be free of a thiourea bond, and is exemplified by a carbon-carbon bond, an amide bond, an ether bond, an ester bond, and the like.

[0035]

The connection between the chelating agent and the linker (L) can be formed, for example, by the reaction of an N-hydroxysuccinimido ester (NHS) group of the following formula (A-7) or (A-8), or a 2,6-dioxotetrahydro-2H-pyranyl group of the following formula (A-9), with the primary amine of linker (L).

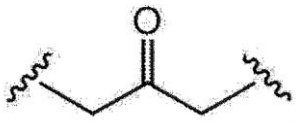
[0036]

more than 3, c is preferably an integer of not less than 3 and not more than 5, and d is preferably an integer of not less than 1 and not more than 3.

[0042]

At least one of Xaa1 and Xaa3 is an amino acid residue derived from an amino acid having a thiol group in the side chain, and Xaa1 and Xaa3 may be the same or different. Examples of the amino acid having a thiol group in the side chain include cysteine and homocysteine. Such amino acid residues are preferably bonded by a disulfide bond, or a sulfide group is preferably bonded thereto via a structure shown by the following formula (4). In the formula (4), the wavy~~broken~~ line indicates the binding part with the sulfide group.

[0043]

(4) 

[0044]

Instead of the aforementioned combination of Xaa1 and Xaa3, one of Xaa1 and Xaa3 may be an amino acid residue derived from an amino acid having a thiol group in the side chain, and the other may be an amino acid residue derived from an amino acid having a haloacetyl group in the side chain. These are bonded via a thioether bond. The terminal of the haloacetyl group is substituted with a halogen such as iodine or the like, and the halogen is eliminated by a reaction with the thiol group in the other side chain, whereby a thioether bond is formed.

[0045]

Specific examples of the amino acid sequence of the antibody-modification peptide represented by the formula (i) include the peptides described in WO 2016/186206, WO 2017/217347 and WO 2018/230257, and these can also be used.

present invention is preferably in the form of an aqueous solution. It is more preferably in the form of a buffer from the aspect of maintaining the radiochemical purity as described above. As the buffer, any buffer used in an antibody drug containing ADC of an anti-HER2 antibody ~~or an anti-HER2 antibody~~ as an active ingredient can be used. As a non-limiting example, histidine buffer or succinate buffer can be used. The histidine buffer is composed of histidine and a salt thereof, for example, histidine and hydrochloride thereof or histidine and acetate thereof. The succinate buffer is composed of succinic acid and a salt thereof, for example, succinic acid and a sodium salt thereof. The radiopharmaceutical of the present invention may contain any sugar such as sucrose or trehalose, and may also contain a solubilizer such as polysorbate 20 and polysorbate 80.

[0113]

The radiopharmaceutical of the present invention can be used for radionuclide therapy of cancer by selecting metal radionuclides that have a therapeutic effect, specifically radionuclide that emits α rays or nuclide that emits β rays (preferably Ac-225, Y-90, Lu-177, more preferably Ac-225). In this radionuclide therapy, the radiopharmaceutical of the present invention is administered by intravenous injection or orally to cause accumulation of the radioconjugate of the present invention in a lesion site such as a cancer primary lesion or metastatic lesion, and cancer cells at the lesion site are destroyed by the radiation emitted from the metal radionuclide. The amount to be administered and dose of the radiopharmaceutical of the present invention is appropriately determined by the efficacy of the active ingredient, the mode and route of administration, the stage of cancer progression, the body type, body weight and age of the patient, and the type and amount of the therapeutic drug used in combination for other diseases.