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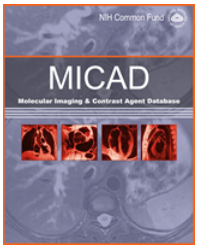

[^{111}In]-Ethylenedicysteine-murine anti-phosphotyrosine antibody

^{111}In-EC-APT

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Chemical name:	[^{111}In]-Ethylenedicysteine-murine anti-phosphotyrosine antibody	
Abbreviated name:	^{111}In-EC-APT	
Synonym:		
Agent Category:	Antibody	
Target:	Bcr-Abl tyrosine kinase	
Target Category:	Enzyme	
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{111}In	
Activation:	No	
Studies:	• Rodents	Click here for the nucleotide and protein sequence of mouse (*Mus musculus*) tyrosine kinase.

Background

[PubMed]

The overexpression or constitutive activation of non-receptor tyrosine kinase (TK) such as Src- and Bcr-Abl is one of the several mechanisms known to initiate and participate in the progression and metastasis of cancer (1, 2). Because of their role in the development of different neoplasms, small-molecule drugs such as imatinib, dasatinib, and others that block TK activity by inhibiting ATP binding to the enzyme are often used to treat patients suffering from this disease (3, 4). Because several different TK blockers are either under development or are being evaluated in clinical trials to treat cancers, it is important to be able to screen patients to determine which TK inhibitor is likely to result in a good prognosis for an individual (5). Although invasive procedures such as biopsies are routinely used to determine the efficacy of an anti-cancer treatment, a noninvasive technique such as imaging would probably be preferred to evaluate drug activity during early stages of the treatment.

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Wu et al. envisioned that antibodies labeled with a radionuclide and directed toward an intracellular non-receptor TK could be used for the noninvasive determination of drug efficacy (5). The investigators evaluated an ethylenedicysteine (EC)-murine anti-phosphotyrosine (APT) antibody labeled with radioactive indium (^{111}In) (^{111}In-EC-APT) to image the Bcr-Abl TK, which is known to be upregulated and to promote chronic myeloid leukemia (6), in a mouse xenograft tumor model. The radiolabeled antibody (Ab) was also used to investigate tumor imaging changes in the animals after treatment with imatinib.

Synthesis

[PubMed]

The synthesis of ^{111}In-EC-APT was described in detail by Wu et al. (5). The various biological reagents used for the studies and described in this chapter, including the control (anti-phospho-Bcr-Abl Ab) and the murine APT 4G10 Abs, were obtained from commercial sources. EC was conjugated to the APT Ab, murine immunoglobulin G_1 (IgG_1), anti-phospho-Bcr-Abl Ab, and bovine serum albumin (BSA) with sulfo-*N*-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) as the coupling agents.

For the conjugation of EC, the various bioreagents were respectively incubated with a mixture of EC, NHS, and EDC for 17 h at room temperature. The purification and final percent yield of the respective EC-conjugated bioreagents and the ratio of chelating agent per antibody molecule were not reported. For labeling with ^{111}In, the radionuclide was mixed with the respective EC-conjugated bioreagent to obtain ^{111}In-EC-BSA, ^{111}In-EC-IgG_1, ^{111}In-EC-Bcr-Abl, and ^{111}In-EC-APT. Purification of the radiolabeled bioreagents was not reported. Radiochemical purity of the ^{111}In-labeled biochemicals was reported to be >95%, as determined with thin-layer chromatography. The specific activity and stability of the various labeled bioreagents were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No references are currently available.

Animal Studies

Rodents

[PubMed]

Tumor imaging studies were performed with immunodeficient mice bearing K562 cell tumors, a human chronic myeloid leukemia cell line that constitutively expresses activated Bcr-Abl TK (5). The mice were divided into five groups, each consisting of five animals. The first group received ^{111}In-EC-BSA to visualize normal blood flow in the tumor; the second group received ^{111}In-EC-APT to determine tumor specificity of the labeled Ab, and the third group was treated with imatinib for 3 days before the ^{111}In-EC-APT injection and during the imaging study (a total of 4 or 5 d). Two other groups of animals received either ^{111}In-EC-IgG_1 or ^{111}In-EC-Bcr-Abl to serve as the negative and positive controls, respectively. Images were acquired at various time points up to 48 h after the radiobiochemical injection.

Determination of the tumor/non-tumor count densities after planar scintigraphy revealed that there was an increased uptake of ^{111}In-EC-APT by the tumors compared with ^{111}In-EC-BSA (5). Mice treated with imatinib showed a reduced ($P < 0.05$) ^{111}In-EC-APT uptake. At 48 h after treatment with the radiotracers, one animal from each group was subjected to single-photon emission computed tomography-computed tomography (SPECT-CT), which produces a dynamic image (for details see Wu et al. (5)) of the combined functional and structural features of the tumor, to measure the precise phosphorylation status of the tumors. Results obtained

with SPECT-CT were similar to those obtained with planar scintigraphy. The tumor/normal muscle count ratios (TMR) were determined for all radiotracers used to treat the animals (5). The TMR ratios were reported to be 1.5, 1.9, 4.0, and 6.0 for ^{111}In-EC-BSA (used to visualize blood flow), ^{111}In-EC-IgG$_1$ (negative control), ^{111}In-EC-APT, and ^{111}In-EC-Bcl-Abl (positive control), respectively.

With results obtained from this study (5), the investigators concluded that imaging could be used to select a specific TK inhibitor for the treatment of certain cancer and to predict the treatment response in a clinical setting (5).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

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