Preclinical study of $^{177}$Lu-DOTA-trastuzumab, a potential radiopharmaceutical for therapy of breast cancer positive HER-2

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Abstract

Anti human epithelial receptor type 2 (HER-2) monoclonal antibody based radiopharmaceutical, $^{177}$Lu-(1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetra acetic acid)-trastuzumab (177Lu-DOTA-trastuzumab), which is expected to be potential for diagnostic and therapeutic agent of breast cancer positive HER-2, with radiochemical purity of > 99% had been successfully prepared. Preclinical studies, which were aimed in providing basic data for clinical trial and in particular in finding out the effectiveness of 177Lu-DOTA-trastuzumab in killing cancerous cells which express HER-2, had been performed. These included urine and faeces clearance tests, imaging with gamma camera and cytotoxicity test. The results of experiment showed that the clearance of radioactivity post injection of 177Lu-DOTA-trastuzumab on normal rats more rapid through urine compared to through faeces. The gamma camera image on normal rat up to 144 hours post injection of 177Lu-DOTA-trastuzumab showed that there was still trace of radioactivity in hepatic area. The residue of radioactivity (< 5%, quantified by bio distribution test) was found to be relatively lower compared to the residue of radioactivity of other reported radiolabelled trastuzumab such as 111In-NSL-trastuzumab. However, this residue of radioactivity has to be taken into a serious consideration when 177Lu-DOTA-trastuzumab is going to be applied on cancerous patients. Cytotoxicity test showed that 177Lu-DOTA-trastuzumab was far more effective in killing cancerous cells positive HER-2 (SKOV-3 cell lines) compared to the unlabelled trastuzumab.

Keywords: breast cancer, 177Lu-DOTA-trastuzumab, preclinical studies, radiolabelled anti-HER-2 monoclonal antibody

Introduction

Cancer has now become one of prominent society health problems. Current report showed that cancer has become the third cause of deaths in Indonesia (Wikipedia). Globocan reported that breast cancer as being the most common type of cancer that has been suffered by Indonesian women (Golobocan, 2008). Globocan also reported that in 2008 in Indonesia, there were 39,831 breast cancer cases with mortality of 20,052. This statistic shows that how cancer has become a heavy burden to our society welfare physically and emotionally.

It has been reported that between 25 - 30% of breast cancer had high expression anti human epithelial receptor type 2 (HER-2) (Tai et al., 2010; Wikipedia; Ross et al., 2004). The existence of HER-2 on cancerous cells, which was reported to be seven time higher compared to those on normal cells, indicated that such breast cancer is an aggressive, tends to metastases, short recurrences and difficult to handle kind of cancer. Expression of HER-2 is also found on other cancers such ovary, gastric, and uterine serous endometrial carcinoma. Clinically HER-2 has been a target for trastuzumab, a humanised monoclonal antibody that is marketed as Herceptin for treatment of breast and gastric cancers positive HER-2 (Baselga 2001a; Baselga 2001b). The inhibition of proliferation cancerous cells by trastuzumab is believed to be caused by the binding of trastuzumab toward HER-2 which in turn stop HER-2 signalling for proliferation process of cells.

Radiopharmaceutical is a pharmaceutical compound which is one or more of its atoms comprise of $\gamma$, $\beta$- and/or $\alpha$ (alfa)-particles emitters (iaea.org). Radipharmaceuticals which content gamma emitting radionuclide are commonly used as imaging radiopharmaceuticals for diagnostic, identification and/ or localisation of cancer. It is also used to predict and to evaluate the progress of a therapy. Radiopharmaceutical with alfa or beta particle emitter is mainly used for internal therapy of cancer. Therapeutic radiopharmaceutical with radionuclides which not only emit alfa or beta particle but also emit an imageable emission is