ASTATINE-211: JAPAN'S STRATEGIC WEAPON AGAINST CANCER

Japan is working to develop a new and interesting ACCELERATOR-BASED RADIONUCLIDE THERAPY.

Researchers in Japan are developing world-leading expertise in making and using the alpha particle emitter, astatine-211 (^{211}At), which has potential for use as a strong radionuclide therapy for treating cancer. Although clinical trials in humans are just beginning, collaborative initiatives are currently looking at astatine-211 in Japan, some European countries, and the United States.

In Japan, Osaka University and Fukushima Medical University (FMU) are among five centres using cyclotron accelerators to make the radionuclide, says Tadashi Watabe, a nuclear medicine physician at Osaka University.

Researchers at these centres hope that the radionuclide will be useful in radiotherapy treatments — one of the three key weapons in our anti-cancer arsenal. Radiotherapy harnesses radiation to kill cancer cells and shrink tumours, explains Watabe, and it's used in the place of, or in combination with, surgery and chemotherapy.

An advantage of alpha particles is that their relatively large mass makes them very effective at damaging DNA and killing cancer cells, with a potency of about five times that of commonly used beta or gamma radiation at the same dose[1].

But alpha particles are also a relatively new option for radiotherapy compared to gamma rays or beta-particles, which have already been used for a long time against cancers. One challenge, explains Watabe, is that alpha particles, unlike some other radiation therapies, cannot be applied externally as their large mass prevents penetration beyond the skin.

Alpha particles are therefore being developed for intravenous administration, or direct injection into affected tissue, in a manner that seeks out and targets the cancer cells. Recently, improved targeting of tumours has been the focus for Osaka University and FMU researchers, with animal models showing positive results in treating pancreatic cancer[2] and malignant adrenal medullary tumours[3].

Fukushima Medical University has been conducting clinical research on astatine-211-based therapy for rare neuroendocrine tumours.

ALPHA THERAPY

Japan has fast become a leader in exploring the potential of astatine-211, which is made by bombarding bismuth with helium in particle accelerators. This expertise has been developed out of necessity as in recent years Japanese nuclear reactors are highly regulated and are not in a position to produce many medical radionuclides. There has therefore been a need to import the alpha emitters used for radiotherapy from other parts of the world, explains Kazuya Kabayama, a radiochemist at Osaka University.

"The Fukushima nuclear accident in 2011 led to our regulations for constructing and operating nuclear reactors becoming much stricter," says Kabayama. That issue, combined with significant public concern about nuclear reactors, has led Japan's government to strongly support the development of the five sites that can make astatine-211 using small-scale cyclotron technology, an area in which Japan is now specializing.

"Japan is now the best place for astatine-211 research for medical uses," Watabe says. "Although other countries, especially the United States and others within Europe, are also moving forward."

In addition to their potency, targeted alpha particle therapies offer a few advantages, he adds. They may mean that patients don't need to be isolated in dedicated rooms as the radiation penetration range and release of associated radiation is low, unlike beta-radionuclide therapy with gamma-ray emission.

Also, the location of astatine-211 can be identified using X-ray imaging, due to the X-rays that are emitted as it decays. The short half-life of astatine-211 (7.2 hours) also ensures the radioactive decay of the treatment falls to virtually zero very quickly, enhancing the ability for safe use.

TARGETING TUMOURS

A promising technique for targeting cancers with astatine-211 is by exploiting the natural selective uptake of some radionuclides into cancerous sites, says Watabe.

However, a more versatile approach is to combine a radionuclide with a small molecule or antibody that will selectively bind to a protein predominantly found in the target cancer cells.

One of the Japanese teams has already reported the results of animal trials targeting rare neuroendocrine tumours with malignant progression, called pheochromocytomas[3]. The study used astatine-211 linked to an analogue of the hormone norepinephrine as the targeting agent.

This carrier molecule is taken up by pheochromocytoma cells due to the increased expression of a norepinephrine transporter protein in the cell membrane. A clinical trial of this therapy, by intravenous injection, is now underway at FMU.

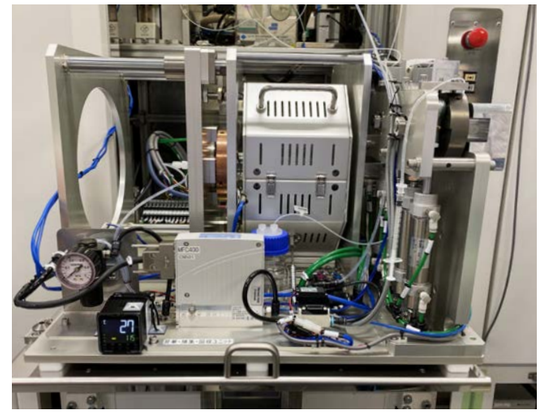
In the meantime, the Osaka University team has been exploring the potential of intravenously administered astatine-211 compounds to treat thyroid[4] and prostate[2] cancer.

For thyroid cancer, the Osaka researchers use a simple ionic molecule of astatine, which can accumulate in the thyroid cancer in a similar manner to the well-established beta particle emitter, iodine-131. This is possible because astatine is in the same group of the periodic table as iodine and therefore has very similar chemical properties, explains Watabe.

If successful, the treatment could be useful to patients using iodine-131 whose cancer has recurred and has become intractable to radioiodine therapy. Using locally produced astatine-211 could also overcome the need to import iodine-131 from abroad, says Watabe.

After tumour shrinkage in animal trials, a Phase I clinical trial in humans is underway. Results are expected in March 2025, which the researchers hope will yield the safety assurance and dosage data needed for the transition to Phase II trials.

For prostate cancer, the Osaka team use their astatine linked to a small peptide molecule that selectively accumulates in the membrane of prostate cancer cells.[5] After positive results in animal models, the researchers plan to begin clinical trials in 2024.



▲ Astatine-211 is made by bombarding bismuth with helium followed by extraction using a device at Osaka University Hospital (pictured) in Japan.

LOCALLY MADE

Developing the potential to use astatine-211 does require a significant investment in infrastructure. The radionuclide only has a 7.2-hour half-life, which means that accelerators producing it must be close to where they will be used, notes Kohshin Washiyama, a radiochemist at FMU. Japan is currently running production sites around the country.

"Given the feasibility of local production, coupled with all of its clinical advantages, we realized about a decade ago that developing facilities to make astatine-211 was the best way forward for us," says Washiyama. The country also wishes to minimize its dependency on expensive imported radionuclides, he adds.

The FMU radionuclide production and clinical research effort is now proceeding in cooperation with the new Fukushima Institute for Research, Education and Innovation (F-REI), which was established by the Japanese government in April 2023. F-REI has extensive plans to support a new scientific innovation area in Fukushima as part of the reconstruction and revitalization after the Great East Japan Earthquake and nuclear disaster.

A new dedicated facility with cyclotron for the mass production of the radionuclide is also under construction at Osaka University, putting the university at the forefront of astatine-211 research, says Watabe. ■

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