JAPAN PIONEERS A NEW CANCER RADIATION TREATMENT

BORON NEUTRON CAPTURE THERAPY is being used in Japan to target and treat head and neck tumours. Many other countries are now building facilities.

In 2020, Japan became the first country to approve boron neutron capture therapy (BNCT), a new highly targeted radiotherapy for cancer.

Like many other radiotherapy options, BNCT directs beams of radiation into the body to kill cancer cells. But BNCT — which uses less intense beams than traditional radiotherapy — makes use of a targeted interaction between boron in the tumour and neutrons in the beam that releases a strong radiation locally, minimizing damage to healthy tissue.

In Japan, BNCT has been approved for the treatment of unresectable advanced or recurrent head and neck tumours, explains Koji Ono, director of the Kansai BNCT Medical Center at Osaka Medical and Pharmaceutical University. Standard treatments such as chemotherapy, other radiotherapies or targeted pharmaceuticals, are still the first choice for head and neck cancer. However, BNCT is now available for more intractable cases, Ono explains.

Across Japan, more than 500 patients with head and neck cancers have been treated using the technology so far, and the numbers of patients are increasing each year.

STRIKING EFFECT

Traditional radiotherapy uses beams of powerful ionizing radiation, such as X-rays or carbon ions, to directly kill tumour cells. BNCT, however, uses a method that does less damage to tissue on its way to the target tumour cells. To do this, patients are given a boron-containing drug designed to accumulate in tumour cells. Shortly after, doctors release a stream of low-energy neutrons using a compact particle accelerator, irradiating the now boron-heavy tumour tissue.

Because low-energy neutrons carry no electrical charge, they don't damage the cells they pass through. The cancer-killing effects of BNCT arises from the destructive alpha and lithium particles that are produced when neutrons strike an atom of boron. So, by ensuring the boron is already inside tumour cells, the cell-killing alpha and lithium particles can be more easily restricted to tumour tissue and avoid damaging healthy cells.

The hope is that cancers beyond those of the head and neck can be treated with BNCT, says Ono. But when tumours sit in deep organs, such as the pancreas and liver, it's challenging to deliver the neutrons to the site of the cancer.

The problem, says Ono, is that the neutrons used for BNCT are a relatively weak form of radiation and can't be applied deep in the body at therapeutic levels. Head and neck cancers are usually near the surface and so are relatively accessible.

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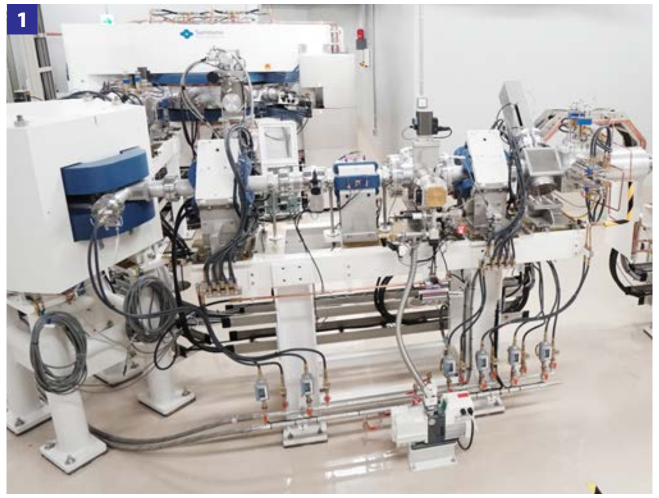

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▲ 1. Boron neutron capture therapy uses an accelerator system (pictured), to produce a stream of neutrons that generates cancer-killing alpha and lithium particles when the neutrons hit boron-laced tumour tissue.

2. A patient is positioned for boron neutron capture therapy, which is being used in Japan to treat advanced or recurrent head and neck cancers.

3. A patient is monitored during boron neutron capture therapy.

HIGHER CONCENTRATION

One potential way to treat deeper tumours is to deliver a higher concentration of boron to cancer tissues. That way, even a weak beam of neutrons can have a therapeutic effect. Existing drugs can make boron preferentially accumulate in tumour cells, compared with normal cells, with a ratio of about 3.5 to 1.0.[1] "If we find a new boron compound that can reach a ratio of 10 to 1, then many other types of cancer could be treated with BNCT," Ono says

One researcher trying to make drugs that can boost the boron uptake of cancer cells is Koki Uehara, President and COO at Stella Pharma Corp in Osaka.

He knows all about boron carrying agents, as Stella produces the only one approved in Japan for BNCT. "We are the only company in the world that provides a drug for this purpose at a pharmaceutical grade," Uehara says.

Several feats of engineering were required to create this agent. Natural boron comes as a mix of two types, but only one of these isotopes — boron 10 — absorbs neutrons. Some 80% of natural boron is the other type, boron 11. Stella Chemifa Corp, which is associated with Stella Pharma, is the only Japanese company that has a way to enrich the boron 10 content of its agents to levels acceptable for BNCT treatment in Japan.

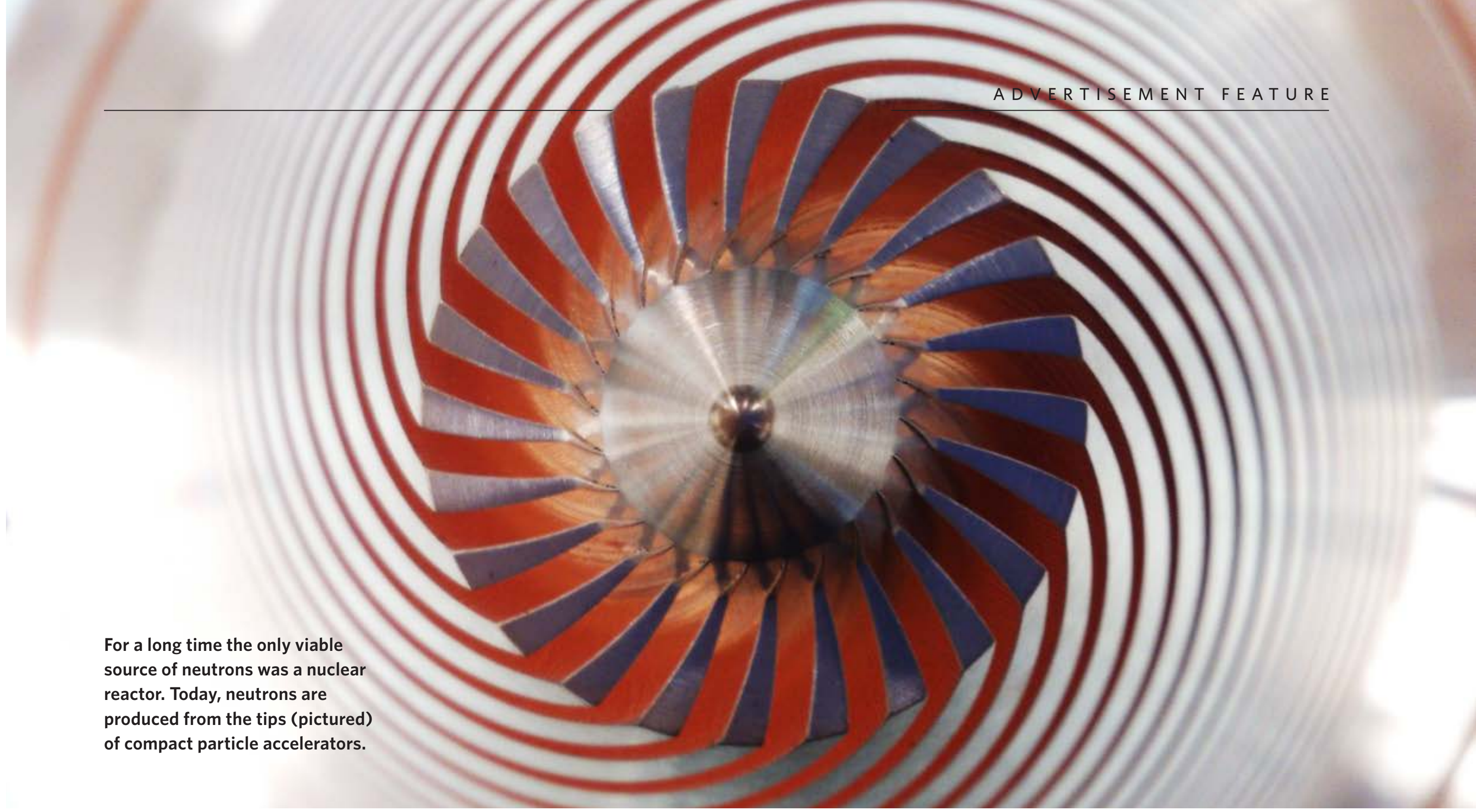
In addition, Stella Pharma Corp has created a structure for the agent that closely resembles phenylalanine, a basic cell metabolite. As phenylalanine is required by tumour cells in large amounts — because of their rapid growth and proliferation — this ensures preferential take-up by cancer cells compared with healthy cells.

However, boron-containing drugs are not very soluble in water, which makes them difficult to administer into the bloodstream in large quantities. For the neutron therapy to destroy cancer cells, tumours must accumulate more than 20 parts per million of boron, so patients must receive a high intravenous dose of about 500 mg per kilogram of bodyweight, or 30 g of the drug for a 60 kg person.[2] Yet, the drug has a solubility in water of just 0.6g/litre, meaning the patient would have to be drip fed more than 50 litres of solution. To get around that, Uehara says the company experimented with additives, eventually discovering a mix that made their agent almost 100 times more soluble. That's the key breakthrough that has made a clinical application of BNCT possible, he says.

THERE ARE NOW 33 BNCT FACILITIES AVAILABLE OR UNDER CONSTRUCTION, IN COUNTRIES FROM THE UNITED KINGDOM TO THAILAND.

Another innovation that has been important to BNCT is the way the neutrons are made, says Hiroshi Igaki, head of the Department of Radiation Oncology at the National Cancer Center Hospital in Tokyo. The theory that BNCT could be used to treat cancer cells was first raised in 1936, just four years after neutrons were discovered. But for decades, the only viable source of neutrons was a nuclear reactor.

That's changed in recent years, with the development of a compact accelerator-based BNCT system. Accelerators use electromagnetic fields or radio frequency electric fields to propel charged particles to very high speeds and energies. Through adjusting the acceleration energy of their system, this process can now be used to produce a stable supply of neutrons, says Igaki.



For a long time the only viable source of neutrons was a nuclear reactor. Today, neutrons are produced from the tips (pictured) of compact particle accelerators.

COMPACT TECHNOLOGY

In Japan, an accelerator-based BNCT system developed by Sumitomo Heavy Industries, Ltd. received regulatory approval in 2020. Other similar devices developed by CICS, Inc. are undergoing clinical trials at the National Cancer Center Hospital. While still complex and expensive, this technology offers a more convenient source of neutrons, says Igaki.

Other countries are catching on. According to the International Atomic Energy Agency, there are now 33 BNCT facilities available or under construction, in countries from the United Kingdom to Thailand.

Researchers in Japan are also exploring whether BNCT can help treat other types of cancer. Igaki has been investigating the use of BNCT to treat a variety of cancers, including a study of patients with scalp angiosarcomas[3], which are cancers of the blood and lymph vessels. He says the outcomes give him some hope for wider use. ■

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