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Drug targets only the cancer cells and spares healthy cells. This means patients at the advanced stages of the disease can live months longer, free of symptoms

When a cure is elusive for an ovarian cancer patient, doctors try to prolong the time she is able to live without the disease worsening.

A targeted cancer drug increases this progression-free survival by two to four months when added to the standard chemotherapy that has changed little in the last decade, recent studies have shown.

The studies have convinced some doctors here to offer this drug called bevacizumab, which goes by the trade name Avastin, to patients when they have been newly diagnosed with advanced ovarian cancer.

This drug was at first offered only to patients whose cancer has recurred because the disease eventually becomes resistant to first-line drugs.

Checks showed that doctors at the National University Cancer Institute, Singapore (NCIS), Parkway Cancer Centre, Raffles Hospital and Thomson Women Cancer Centre are now offering Avastin to patients who are newly diagnosed with advanced cancer or have had a relapse.

At KK Women's and Children's Hospital (KKH) and Singapore Medical Group's The Cancer Centre, the drug is given only to women whose cancer has recurred and is not responsive to conventional chemotherapy.

The National Cancer Centre Singapore (NCCS) declined to comment.

In the last five years, oncologists have put more than 100 ovarian cancer patients here on the drug.

Avastin has been approved by the Health Sciences Authority for treating advanced cancer of the colon, breast, lung, kidney and glioblastoma (cancer of the central nervous system).

Its use in ovarian cancer patients is pending approval.

A spokesman explained: "In clinical practice, the use of a drug may precede regulatory approval if, in the professional judgment of the doctor, the treatment is clinically justified."

Last December, Avastin, made by Swiss drug company Roche, received European approval for use in the front-line treatment of advanced ovarian cancer, based on results from two studies.

Doctors said they are awaiting results from further ongoing trials on Avastin to see if the longer progression-free survival period may eventually lead to an improvement in overall survival rate. This would warrant the use of Avastin as standard treatment for ovarian cancer.

Meanwhile, doctors agree that the use of Avastin is already beneficial for ovarian cancer patients because most of them are diagnosed only when the disease is advanced and unlikely to be cured.

Ovarian cancer is usually not detected early because no reliable screening tool for it exists and its symptoms, such as marked swelling of the abdomen, typically surface late.

Each year, more than 250 women are diagnosed with ovarian cancer and about 90 die

where in stages 3 and 4.

At stage 3, the cancer has spread beyond the pelvis to the lining of the abdomen, which is called the peritoneum.

At stage 4, the most advanced stage, the cancer has spread to the liver, lungs or other organs located outside the peritoneal cavity.

Dr Tay Eng Hseon, medical director of Thomson Women Cancer Centre, estimated that only one in four of patients with cancer in stage 3 or 4 lives at least five years after diagnosis.

In contrast, up to nine in 10 of those who were diagnosed in stage 1 of the disease reach the five-year survival mark.

Dr Lynette Ngo, a consultant at Raffles Cancer Centre at Raffles Hospital, said that between 70 and 80 per cent of patients with advanced ovarian cancer suffer a relapse.

When it happens, they face the prospect of requiring treatment for the rest of their lives, she said.

HOW THE DRUG WORKS

The standard treatment for ovarian cancer is surgery followed by chemotherapy using platinum-based drugs. Some patients are put through chemotherapy first if they are not deemed fit for surgery.

Dr Lim Sheow Lei, a consultant from the department of gynaecological oncology at KKH, said Avastin works differently from platinum-based chemotherapy drugs that kill rapidly growing cells in the body.

These include cancer cells and some healthy cells such as those in the bone marrow, digestive tract and hair follicles, giving rise to side effects such as a suppressed immune system, nausea, vomiting and hair loss.

Avastin, on the other hand, attacks the Achilles' heel of cancer cells that controls their growth and development, Dr Lim said.

The drug acts by binding with vascular endothelial growth factor, a protein that helps initiate the growth of new blood vessels that feed the tumour, in a process known as angiogenesis.

Avastin "starves" the tumour and causes it to shrink and stop growing, Dr Lim said.

This protein is produced in low quantities in healthy cells, but in large quantities by certain types of cancer cells, so the drug targets these cancer cells and hardly affects the healthy ones.

So the spread of the cancer is stopped more effectively when Avastin is combined with conventional chemotherapy drugs.

In one study, 1,873 patients who had been newly diagnosed with advanced ovarian cancer were randomly divided into three groups.

They were all given six cycles of platinum-based chemotherapy drugs carboplatin and paclitaxel, but two groups were also given Avastin.

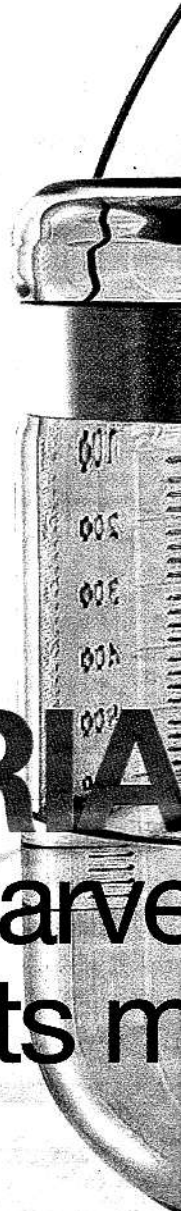
In those who received Avastin with chemotherapy followed by Avastin alone for a year, the cancer did not progress for a median of 14.1 months, longer than the 10.3 months for those who had chemotherapy with a placebo and continued with the placebo for a year.

This worked out to a 28 per cent reduction in the risk of progression with the use of Avastin.

Patients who received Avastin with chemotherapy but not afterwards were progression-free for a median of 11.2 months.

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AVASTIN CAN COST \$8k PER DOSE, ON TOP OF THE COST OF CHEMOTHERAPY





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months of completion of treatment – showed that the risk of cancer progression was reduced by 52 per cent in those who received Avastin and chemotherapy, compared to those given only chemotherapy.

Women given Avastin had their cancer growth halted for a median of 6.7 months, longer than the 3.4 months in those who had chemotherapy alone.

This means a minority of patients will have their cancer in remission, while others do not have their symptoms worsening.

Some of the symptoms of ovarian cancer are abdominal pain, bloating, indigestion and constipation or diarrhoea.

Dr Lim Siew Eng, a senior consultant at the department of haematology-oncology at NCIS, said controlling cancer longer, even for only a few months, is significant for patients.

She said: "When they are not under the shadow of active cancer, they have a higher quality of life."

HEFTY PRICE TAG

Studies also showed that the use of Avastin led to a higher risk of side effects such as hypertension and gastrointestinal perforation.

But the authors noted that "although bevacizumab use resulted in additional toxic effects, it was not associated with a decline in quality-of-life scores".

Doctors here said hypertension was the most common side effect reported by their patients on Avastin, but it was easily controlled with medication.

To avoid the risk of gastrointestinal perforation, patients who have had extensive bowel surgery or whose cancer has invaded the intestines are not put on the drug, Dr Ngo said.

Still, the take-up rate of Avastin is low because it comes with a hefty price tag.

Dr Lim, from NCIS, estimated that out of every 10 patients offered the drug, only two to three go for it.

At a public hospital, each dose of the drug can add an additional \$4,000 to \$8,000 to one cycle of chemotherapy, which costs between \$1,500 and \$2,000.

For example, at KKH, where 10 patients have been receiving

Avastin each year since 2008, a dose of Avastin costs \$4,000 onwards.

Dr See Hui Ti, a senior consultant at Parkway Cancer Centre, estimated that Avastin can cost patients between \$5,000 and \$6,000 per dose, on top of each cycle of chemotherapy, which costs between \$2,000 and \$4,000.

But her patients would "sooner or later" agree to be put on Avastin as their cancer would become increasingly difficult to control, she said.

Dr Ngo recalled seeing, two years ago, a 43-year-old woman with ovarian cancer that had relapsed eight months after treatment was completed.

She went to NCCS, where Dr Ngo was working then, in a wheelchair because her legs were swollen, the result of poor blood flow caused by cancer.

Her abdomen was distended and painful from fluid that had accumulated as a result of the cancer spread in the lining of the abdominal cavity.

She also had a tumour the size of a tennis ball jutting out of her neck, where the cancer had also spread.

Her cancer shrank during the 1½ years that she was put on the intravenous infusion of Avastin, given once every three weeks. She also had chemotherapy for the first four months.

Unfortunately, her tumour grew larger last year and so the Avastin treatment was discontinued.

But during the time when she was on Avastin, the housewife was well enough to be taken off painkillers and to continue doing housework.

"She was symptom-free and it was as if she had no

administered
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More patients reach the five-year survival mark

More women with ovarian cancer here are still alive five years after diagnosis, even as more are struck by it and diagnosed when it is at an advanced stage.

The proportion who reached the five-year survival mark – often seen as equivalent to being cured – was 51.1 per cent between 2006 and 2010. It is the first time in over three decades that long-term survivors have formed the majority.

The five-year survival rate has been rising from 28.9 per cent between 1978 and 1982, to 45.8 per cent between 2003 and 2007, the Ministry of Health's (MOH) National Registry of Diseases Office reported.

Doctors are heartened by the improvement as they mark Ovarian Cancer Awareness Month, which ends on Saturday.

They say it can be attributed to an increase in awareness of the symptoms of ovarian cancer, more skilful surgeons and more drug choices over the years.

Dr Lim Siew Eng, a senior consultant at the department of haematology-oncology at the National University Cancer Institute, Singapore (NCIS), said the challenge of detecting ovarian cancer is that it has "insidious symptoms which are common to healthy people".

These include abdominal pain, bloating, indigestion and a change in bowel habits such as constipation or diarrhoea.

Dr See Hui Ti, a senior consultant at Parkway Cancer Centre, noted that doctors in the community are now more likely to have a high index of suspicion when women go to them with these symptoms, putting them through tests for early detection.

In the last two decades, the extent of surgery done – the mainstay of treatment to remove as much of the tumour as possible – has improved patients' outcome, doctors observed.

Dr Tay Eng Hseon, medical director of Thomson Women Cancer Centre, noted that doctors would typically remove only the ovaries and uterus in the past.

Now, they are technically skilled to handle radical surgery that involves removing part of the intestines, the lining of the abdomen called the peritoneum, the membrane covering the stomach called the omentum, and lymph nodes, he said.

Another possible reason for better surgical outcome is that patients are increasingly operated on by gynaecologic oncologists – surgeons trained in managing

general surgeons, said Dr Lynette Ngo, a consultant at Raffles Cancer Centre at Raffles Hospital.

At NCIS and KK Women's and Children's Hospital, surgery on ovarian cancer patients is performed by such specialists.

Dr Ngo cited a study of 3,067 patients, published in the *Journal Of The National Cancer Institute* in 2006, which showed that ovarian cancer patients treated by gynaecologic oncologists had "clearly superior outcomes" than those treated by general surgeons.

At 30 days after the most extensive surgery, 2.1 per cent of those treated by gynaecologic oncologists died, while 4 per cent among those treated by general surgeons died.

Following surgery, most patients are put on chemotherapy to kill stray cancer cells and reduce the risk of a relapse. Platinum-based chemotherapy drugs became available in the 1980s and the combination of paclitaxel and carboplatin has been used routinely as the standard first-line chemotherapy for ovarian cancer since 2003, Dr See said.

As ovarian cancer responds well to these drugs, they also helped improve survival rates, she said.

This is even though more women are being diagnosed with the disease – the fifth most common women's cancer here – and at a later stage.

Ovarian cancer struck 12 in 100,000 women between 2006 and 2010, up from six in 100,000 between 1968 and 1972.

Between 2007 and 2010, 52.3 per cent of ovarian cancer cases were diagnosed in stages 3 and 4, up from 48.8 per cent in the preceding four years.

Doctors say the increase in the number of cases is due to longer life expectancy and falling fertility rates over the years.

Research has shown that women who are obese, have never given birth, have a family history of ovarian cancer and have battled other types of cancer are at higher risk of developing ovarian cancer.

Those who have two or more children, breastfed and used contraceptives for five or more years have their risks reduced.

Unfortunately, there is no effective screening test. MOH recommends women at high risk to go for annual pelvic examination and vaginal ultrasound, with the option of a blood test for a tumour marker called CA 125.

But "there is currently still insufficient evidence to ascertain the effectiveness of screening", the MOH spokesman said.