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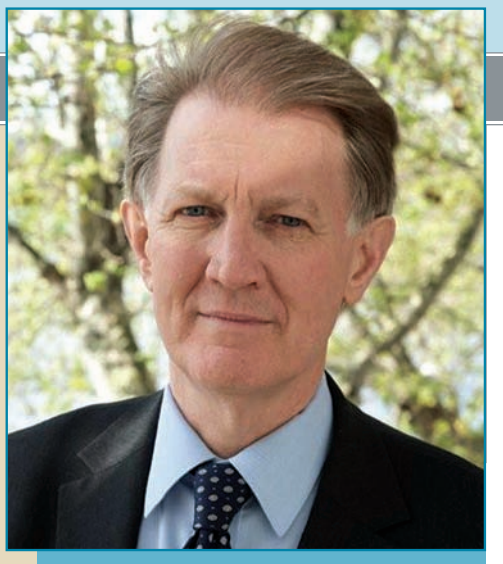
NHS restructure: how the Big Society approach puts cancer first on the strategy list



The health secretary has announced plans for a complete restructuring of the health service, to be achieved through a series of outcome strategies. First on the list is cancer: *Oncology Times* reviews the strategy and asks cancer tsar Mike Richards how he sees it working

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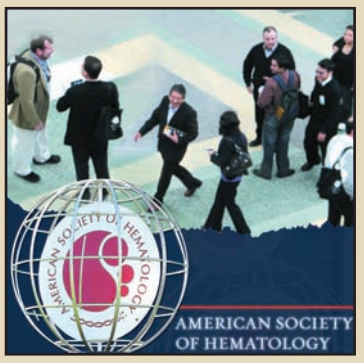
ASH plenary study shows rituximab delays need for chemotherapy in follicular lymphoma patients



For patients with newly diagnosed follicular lvymphoma, a course of rituximab followed by rituximab maintenance approximately doubled the number of patients not requiring chemotherapy or radiotherapy at three years, compared with watchful waiting

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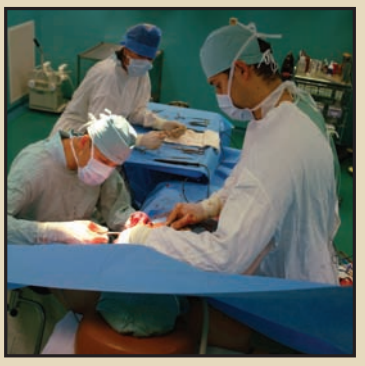
How breast-conserving therapy can lead to better survival rates than mastectomy



A large study of women with newly diagnosed breast cancer has shown that those who underwent breast-conserving therapy had better outcomes than those who had mastectomy

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How do I treat… …a patient with metastatic colorectal cancer?

In the third of our series of personal views from experts, Dr Axel Grothey discusses how he treats metastatic colorectal cancer

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SABCS

CTRC-AACR SAN ANTONIO BREAST CANCER SYMPOSIUM

AZURE results show that adjuvant use of zoledronic acid fails to extend survival in stage II/III breast cancer

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CONFERENCE AND COURSE LISTINGS

ON PAGE 22 AND 23

News:

ASH ANNUAL MEETING

Brentuximab shows high response rates in relapsed/refractory lymphomas

■ Hodgkin's lymphoma patients who do not respond after autologous transplant and high-dose chemotherapy typically have a dismal prognosis. But researchers in a pivotal Phase II trial of brentuximab vedotin reported encouraging activity in heavily pretreated patients with relapsed or refractory disease.

By Robert H Carlson

According to a Phase II trial – presented in Orlando at the American Society of Hematology Annual Meeting – and based on investigator assessment, 34% of 102 Hodgkin's lymphoma patients had a complete response to the antibody-drug conjugate brentuximab vedotin (SGN-35), and 94% had a reduction in tumour size.

The overall response rate in the study was 75%, with a median duration of 29 weeks, and the B symptom resolution rate was 83%.

In another study at the meeting, of patients with relapsed or refractory systemic anaplastic large cell lymphoma, brentuximab vedotin was associated with an 85% response rate – mainly complete remissions.

'This drug has benefited many patients who otherwise were headed for hospice, and has the potential to change the treatment paradigm for relapsed or refractory Hodgkin's lymphoma', said first study author, Dr Robert Chen, assistant professor of haematology and haematopoietic cell transplantation at City of Hope National Medical Center.

Dr Chen said that three patients had gone on to allogeneic transplant by the time data were logged for the presentation, with no mortality at this time, and currently there appears to be no difference in responses by relapsed or refractory status.

Dr Anas Younes: 'The potential impact on years of life saved is huge, because the median age for this disease is only 32'

Antimicrotubule agent

Hodgkin lymphoma is characterised by the presence of CD30-positive Hodgkin Reed-Sternberg cells. Dr Chen explained that brentuximab delivers a highly potent antimicrotubule agent, monomethyl auristatin E, to CD30-positive malignant cells by binding specifically to CD30 on the cell surface. The monomethyl auristatin E is released inside the cell via lysosomal degradation.

Binding of monomethyl auristatin E to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumour cell.

Dr Chen pointed out that an earlier clinical trial had shown that the CD30 antibody alone produced no objective responses among 38 Hodgkin lymphoma patients.

In a Phase I study with brentuximab vedotin given every third week, published in November (Younes et al; NEJM 2010; 363:1812-1821), 11 of 12 patients treated at the maximum tolerated dose of 1.8 mg/kg had tumour reductions, and six of 12 achieved an objective response comprising complete and partial remissions.

The pivotal Phase II single-arm study was conducted at 26 centres to evaluate the efficacy and safety of brentuximab vedotin in Hodgkin lymphoma patients who had relapsed or were refractory after autologous stem cell transplant. The dosage was 1.8 mg/kg every three weeks by IV infusion in the outpatient setting, with up to 16 cycles of treatment given.

Primary endpoint

The primary endpoint was overall response as assessed by an independent review facility according to the Revised Response Criteria for Malignant Lymphoma. Besides previous autologous stem cell transplant, patients had undergone a median of four prior chemotherapy regimens.

The patients' median age was 31 (range of 15 to 77); 53% were female; ECOG performance status at baseline was 0 or 1; more than 70% of patients had primary refractory disease (defined as failure to achieve a complete response or having disease progression within three months of completing frontline therapy); and 39% of patients had lymphoma refractory to the most recent salvage therapy excluding autologous stem cell transplant.

'To date, five patients have received an allogeneic stem cell transplant as their first therapy after discontinuing treatment in the study', Dr Chen said, adding that all of these patients remain in follow-up.The estimated 12-month overall survival rate is 88%.

Dr Robert Chen: 'This drug has benefited many patients who otherwise were headed for hospice, and has the potential to change the treatment paradigm for relapsed or refractory Hodgkin's lymphoma'

Toxicities

Most treatment-related adverse events were Grade 1 or 2. Common treatment-related events of any grade were peripheral sensory neuropathy (47%), fatigue (46%), nausea (42%), upper respiratory tract infection (37%), diarrhoea (36%), pyrexia (29%), neutropenia (22%), vomiting (22%), and cough (21%).

Grade 3 and 4 adverse events reported in more than five patients were neutropenia (14% Grade 3, 6% Grade 4), peripheral sensory neuropathy (8% Grade 3), thrombocytopenia (6% Grade 3, 2% Grade 4), and anaemia (5% Grade 3, 1% Grade 4).

Eighteen patients (20%) discontinued treatment due to an adverse event.

First new Hodgkin's agent in 30 years

The paper's senior author, Dr Anas Younes, professor in the division of cancer medicine at the University of Texas MD Anderson Cancer Center, pointed out in a telephone interview before the meeting that there had not been a new drug for Hodgkin lymphoma in 30 years.

'The potential impact on years of life saved is huge, because the median age for this disease is only 32', said Dr Younes.

'Brentuximab delivers a highly potent antimicrotubule agent, monomethyl auristatin E, to CD30-positive malignant cells by binding specifically to CD30 on the cell surface. The monomethyl auristatin E is released inside the cell via lysosomal degradation. The binding to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumour cell'

About 80% of all Hodgkin's lymphoma patients achieve long-term remission with standard chemotherapy regimens, which may also include radiation therapy, Dr Younes said. And for those who are not cured with front-line therapy, prognosis remains poor, especially for those whose disease relapses after autologous stem cell transplantation.

Dr Ginna Laport said she was impressed by the very manageable side-effects. 'The few patients of mine who went on this trial did not have to stop due to peripheral neuropathy.... Brentuximab potentially could have a great impact in lymphoma treatment, certainly in patients who relapse after transplant and who have no other options. For an agent to show a 35% complete remission rate and 94% rate of tumour reduction, it's a big breakthrough for this population'

Manageable side-effects

At an ASH media conference highlighting noteworthy presentations, moderator Dr Ginna G Laport, associate professor of medicine in the division of blood and marrow transplantation at Stanford University Medical Center, said she was impressed by the very manageable side-effects of this targeted therapy.

Peripheral neuropathy is an issue with brentuximab vedotin, she said, but is tolerable when the drug is given once every three weeks. And it is easy to give on an outpatient basis.

'The few patients of mine who went on this trial did not have to stop due to peripheral neuropathy', she said.

And Dr Laport added that some of those patients achieved complete responses, even after failed autologous transplants and high-dose chemotherapy.

'Brentuximab potentially could have a great impact in lymphoma treatment, certainly in patients who relapse after transplant and who have no other options.

'For an agent to show a 35% complete remission rate and 94% rate of tumour reduction, it's a big breakthrough for this population.'

Dr Laport also pointed out that other patients at Stanford have been on brentuximab vedotin trials for other histologies such as anaplastic large-cell lymphoma.

Anaplastic large-cell lymphoma

CD30 is also expressed in cells in anaplastic large-cell lymphoma, one of the most common lymphomas in the paediatric population.

Another report at the meeting described very promising results in adult anaplastic large-cell lymphoma with brentuximab vedotin. Among 58 patients (median age of 52), the overall response rate was 86% by independent review facility, including a 53% complete response and 33% partial response; overall response by investigator assessment was 81% – 59% complete and 22% partial.

Tumour reduction was seen in 97% of patients, and 14 of 15 patients with malignant cutaneous lesions had complete resolution, said first author Dr Andrei Shustov, assistant professor of medicine in the division of haematology at the University of Washington School of Medicine in Seattle.

B symptoms resolved in nine of 10 patients who had these symptoms at baseline, he said, and 14 of 58 patients went on to autologous or allogeneic transplant.

Standard therapy for newly diagnosed disease is CHOP, but that regimen fails in about half of patients, Dr Shustov said in an interview.

'Once patients relapse, the majority will die of their disease, because there are no effective salvage treatments', Dr Shustov added.

Dr Andrei Shustov: 'Brentuximab showed responses and durability of responses in the anaplastic large-cell lymphoma population that we have not seen before, with any combination chemotherapies. It's an agent to move into the frontline treatment with hopes of curing a more substantial number of patients'

'Brentuximab showed responses and durability of responses in anaplastic large-cell lymphoma that we have not seen before, with any combination chemotherapies. It's an agent to move into the frontline treatment with hopes of curing a more substantial number of patients.'

'Although lenalidomide and bortezomib also have activity in T-cell lymphomas, as shown in very small, single-institution studies, the activity doesn't even come close to the responses we have seen with brentuximab vedotin'

Approximately half of the study patients were female; the median number of prior chemotherapy regimens was two; and eight patients had not responded to previous autologous haematopoietic stem cell transplantation.

As in Dr Chen's Hodgkin's lymphoma study, the brentuximab vedotin dosage was 1.8 mg/kg administered every three weeks as a 30-minute outpatient IV infusion for up to 16 cycles of treatment.

Peripheral sensory neuropathy

Dr Shustov said peripheral sensory neuropathy of any grade was one of the more common side-effects in this Phase II trial, in 38% of patients, but it was reversible in half the patients and there were no Grade 4 neuropathies. The median time to onset of peripheral neuropathy was 16.9 weeks (six cycles), suggesting that it has a cumulative effect, he said, although there were a few incidents of peripheral neuropathy in the first three or four cycles.

'It was not, by any means, the worst neuropathy that we see with other anti-tubulin agents, or with the vinca alkaloids that are part of the CHOP therapy', Dr Shustov said.

Other common adverse events were nausea (in 38% of patients), diarrhoea (29%), pyrexia (33%), dyspnoea (30%), fatigue (34%), insomnia (23%), rash (21%), and neutropenia (21%).

Grade 3/4 adverse events related to brentuximab were rare: Grade 3 neutropenia occurred in 12% of patients, Grade 4 in 9%; Grade 3 peripheral sensory neuropathy in 10%; and Grade 3 anaemia in 7% of patients.

No treatment-related deaths were reported, but seven patients (23%) discontinued treatment due to an adverse event.

Dr Shustov pointed out that although lenalidomide and bortezomib also have activity in T-cell lymphomas as shown in very small, single-institution studies, the activity 'doesn't even come close to the responses we have seen with brentuximab vedotin, which is the same thing we can say for Hodgkin lymphoma in Dr Chen's presentation'.

Research funding for both studies was provided by brentuximab's manufacturer, Seattle Genetics, Inc.