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Double-pronged attack could treat common children's cancer

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A dual-pronged strategy using two experimental cancer drugs together could successfully treat a childhood cancer by inhibiting tumour growth and blocking off the escape routes it uses to become resistant to treatment, finds a new study.

Scientists at The Institute of Cancer Research, London, found that combining two separate molecularly targeted therapies could stop processes driving growth in a cancer called rhabdomyosarcoma, a major cause of cancer death in children.

The drugs, called AZD8055 and AZD6244, block two different signalling pathways involved in cancer growth – acting like road-blocks on two separate routes that cancers could otherwise use to evade treatment.

The study, published in *Clinical Cancer Research* today (Friday, 1 November), was funded by the NIHR Biomedical Research Centre for Cancer at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (ICR), with additional funding from Cancer Research UK, The Royal Marsden Hospital Charitable Fund and the Chris Lucas Trust.

Rhabdomyosarcoma tumours can form anywhere in the body and resemble primitive muscle tissue. Despite advances in treatment options, there has been little improvement in outcome for patients with rhabdomyosarcoma in decades and they remain difficult to treat.

Previous research has shown that many rhabdomyosarcomas display activity of the PI3 Kinase signalling pathway, which plays a key role in cancer growth. However, blocking this pathway in other cancer types can lead to alternative signalling pathways becoming active to compensate, allowing resistance to treatment to develop.

In this study, scientists at the ICR targeted the PI3 Kinase pathway and a second pathway called MAP Kinase, to assess any compensatory signalling and determine if blocking both pathways could effectively inhibit rhabdomyosarcoma cell growth.

The researchers found that the PI3 Kinase pathway was active in 83% of rhabdomyosarcoma samples from patients, and that 43% of these also showed activation of the MAP Kinase pathway. In experiments on rhabdomyosarcoma cells to block either pathway alone, they saw compensatory signalling through the alternative pathway, suggesting that inhibiting both pathways is an essential approach to treatment, irrespective of whether MAP kinase signalling was initially activated.

The researchers tested rhabdomyosarcomas with drugs known to be effective against the PI3 Kinase and MAP Kinase pathways. When they tried the drugs AZD8055 and AZD6244 separately they saw reduced cell growth and a decrease in levels of markers showing the activity of the signalling pathways. However, compensatory activity was clearly evident.

But when they combined the two drugs they found a synergistic effect, with cell growth reduced to a greater extent than with either treatment alone. They saw similar synergistic results when AZD8055 and AZD6244 were used together in mice with rhabdomyosarcoma tumours, with tumour marker levels reduced to less than 30% of those in controls.

Co-author Dr Janet Shipley, Team Leader in Sarcoma Molecular

Pathology at The Institute of Cancer Research, said:

"Rhabdomyosarcoma is the main type of sarcoma to affect children and little improvement has been made recently using conventional treatments like chemotherapy and radiotherapy - survival rates for some patients with this disease remain bleak. More effective targeted treatment is desperately needed. Our study shows that treating with one or other of these two drugs is not a good strategy but that combining them is a very promising option."

Co-author Dr Jane Renshaw, Senior Scientific Officer at The Institute of Cancer Research, said:

"We found that while most rhabdomyosarcoma tumours seem to have active PI3K signalling, inhibiting this pathway alone isn't enough to be an effective treatment. Cross-talk between the PI3 Kinase and MAP Kinase pathways means that cancer is able to find an alternative route, like traffic finding a way around a road-block. Targeting both pathways using two drugs together stops that compensatory action.

"These two drugs are being tested for use against cancers in adults so the next step will be to progress with clinical trials for children using the dual approach."

Nell Barrie, Cancer Research UK's Senior Science Communication Manager, said:

"Understanding the inner workings of cancer cells is crucial to finding the best ways to tackle the disease. This lab research emphasises the importance of targeting each cancer's weak points and combining drugs to develop more effective treatments – which are urgently needed to improve survival for children's cancers like rhabdomyosarcoma. Further research and clinical trials will shed light on whether this promising drug

combination could help save more lives."

More information: clincancerres.aacrjournals.org/content/19/21/5940

Provided by Institute of Cancer Research