news

Eisenbrand agrees that the relatively broad specificity of some indirubin derivatives has great therapeutic potential. 'It is increasingly clear that attacking a single molecular target in cancer cells rarely works because the cells can often circumvent such inhibition.' Eisenbrand now has indirubin derivatives that inhibit CDKs, Stat3 and the VEGF receptor, a component of the pathway that drives tumor angiogenesis, and hopes to take some of these multifunctional derivatives into early clinical trials next year in collaboration with Faustus Forschung Translational Drug Development AG (Vienna, Austria).

Not just anticancer agents

CDK inhibitors based on indirubin could also have therapeutic uses outside the cancer field, for example, in the treatment of parasitic diseases. In this case, derivatives will have to be designed that inhibit the parasite's CDK while leaving the host's CDKs unscathed. Researchers at Keele University and Aberdeen University, for instance, are trying to develop indirubin derivatives specific for CRK3, a CDK from Leishmania mexicana. And Endicott and her collaborators have been examining the crystal structures of indirubin derivatives bound to pfPK5, one of the malaria parasite's CDKs. 'We have no current plans to develop any indirubin derivatives as antimalarial agents,' stresses Endicott, 'but there may be potential in future to take some of the derivatives that have been designed as anticancer agents and investigate their use in this context.'

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UK government guidance on Alzheimer's drugs postponed

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Recently the National Council for Clinical Excellence (NICE) announced that it was delaying publishing its guidance document on the long term benefit of drugs used for the treatment of Alzheimer's disease (AD). Their earlier review of studies assessing short term benefits of these compounds agreed with the manufacturers' conclusions that there was evidence to suggest a benefit to patients. However, last year, NICE issued a call for a review of the long-term benefits of the compounds. They were concerned that the effects in the shorter studies were, at best, quite modest. More data was needed to assess if this benefit was sustained over longer periods. In March 2005 they published their draft report, which concluded that the drugs were of little long-term benefit. The report provoked vigorous protests from patient groups such as the Alzheimer's Society and strong rebuttals from the companies involved.

No justification

Two classes of drugs were involved in this assessment. Aricept®, Exelon®, and Reminyl® all act by raising brain levels of acetylcholine by blocking its breakdown by the enzyme acetylcholinesterase (AChE). Ebixa® (also sold as Axura®) acts by reducing over-activation of the NMDA glutamate receptor, and is the only product with this mechanism licenced for AD.

The NICE report in March 2005 concluded that the longer term use of the compounds only delayed the time for a patient to go to full-time care was only in the order of one month when measured over a five-year period. This, they concluded, did not justify their use either in terms of side effect burden to the patient nor in the cost of the treatment regime. They were due to publish their official guidance early in July but have decided to engage in further consultation with the pharmaceutical companies.

The drug companies that make these medicines including Lundbeck, Pfizer, Novartis, and Shire have argued that the drugs do show beneficial effects in individual patients which will always be lost in the averaging out that occurs in such large studies. Companies and patient groups also argue that the benefits to individual patients in terms of quality of life were not adequately captured in the report.

Concerns

This news will provide a strong incentive to those involved in trying to predict which patients are likely to respond to particular treatments. Genetic or other markers that would identify patients who will respond best to different classes of drugs or even individual drugs would help doctors to identify those patients in advance that will benefit from taking these drugs.

> **'...the drugs were of little long-term benefit'**

The concern for companies is that this report risks raising the bar for much-needed drugs to an unacceptably high level. The cost of a clinical development program that was required to show efficacy over years would simply make the cost of any drug for Alzheimer's prohibitively expensive.

This is the second blow for Alzheimer's disease patients in a year. Earlier this year the FDA put a black box warning on the off-label use of atypical antipsychotics (Abilify, Geodon, Risperdal, Zyprexa) for the control of psychotic symptoms in AD patients. Their review found that the mortality rate was increased in patients receiving these treatments.

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