News Editor: Matthew Thorne
m.thorne@elsevier.com

news

Predicting ovarian tumor response

Vida Foubister, vfoubister@optonline.net

Scientists at Yale University have teamed up with a Pittsburgh-based biomedical company to develop a screening test that could help physicians determine which drug or combination of drugs will most effectively treat a patient with recurrent ovarian cancer.

Ovarian cancer

More than 16,000 women die from ovarian cancer (Figure 1) each year and there are nearly 26,000 new diagnoses annually in the United States alone, according to American Cancer Society estimates. However, the disease lacks a reliable mechanism for early detection. 'There's no test and there are no early symptoms that are specific enough for people to say, 'Aha, this is ovarian cancer,' explains Judith Wolf, Associate Professor, Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center.

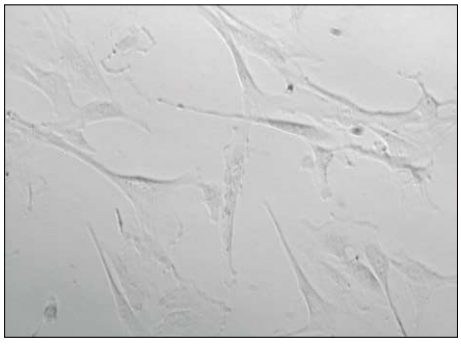


FIGURE 1.
Ovarian tumor cells growing in culture. Image courtesy of G. Mor of Yale University, New Haven, Conn.

This means that about 75% of ovarian cancer patients are identified with stage III or stage IV disease [1]. Although the majority of these women will go into remission following conventional treatment, which typically includes surgery to remove the tumors and then chemotherapy using carboplatin and paclitaxel, the cancer recurs in about 80% of patients.

'When it recurs, in the majority of cases it's chemoresistant,' says Gil Mor, Associate Professor, Department of Obstetrics and Gynecology, Reproductive Immunology Unit, Yale University. 'It's very difficult to know what drugs to use in order to treat patients with recurrent disease. Usually, it's left to the guesswork of the treating physician and his art of combining different drugs.'

Chemosensitive and chemoresistant tumors

In some cases, the initial chemotherapeutic agents used to treat ovarian cancer will be effective in the recurrent disease. Patients with tumors resistant to these drugs turn to 'second-line agents' that either are approved for this indication or are being used off-label due to their demonstrated activity. 'Just about all of them have published response rates of around 20%,' says Wolf. 'The problem becomes, if you have a patient with recurrent ovarian cancer, how do you pick the drugs that the patient is more likely to respond to?'

This is where the screening assay, now being tested in a 12-site clinical trial, would come into play. Yale scientists studied the apoptotic, or cell death, response of ovarian cancer cells and discovered that chemosensitivity is found only when apoptosis is induced [2]. Using a protein that is activated in the final stage of cell death, called caspase-3, they completed a pilot study to assess the potential of an in vitro test to predict the clinical response of 13 patients to chemotherapy. They found that the cells of five out of seven chemosensitive patients had increased caspase-3 activity in response to both carboplatin and paclitaxel, while five of six chemoresistant patients did not show caspase-3 activity in response to one or neither agent [1].

Because of the imperfect correlation between the *in vitro* test and patient sensitivity, they are combining the 'Yale apoptosis assay' with the 'ChemoFX assay,' a proprietary method developed by Precision Therapeutics that assesses the ability of a drug to stop tumor growth, in the current prospective blinded trial. Currently, 36 patients are enrolled in the study and researchers plan to enroll a total of 127 patients by September 2005.

Just another assay?

Oncotech, a Tustin- (California, USA) based oncology company, already offers chemoresistance assays for a number of cancers, including the most popular commercially available assay for recurrent ovarian cancer. Wolf, however, says its validity has not been demonstrated and she questions whether cells growing 'in a vacuum on a plastic dish' can represent the true reaction of a tumor within the body. 'If we don't really know it works, it gives false hope to patients,' she says.

The Yale/Precision Therapeutics trial will analyze a total of five drugs and drug combinations at concentrations that 'correlate

1359-6446/04/$ – see front matter PII: S1359-6446(04)03400-8

news

with the pharmacological concentrations in the blood of patients being treated,' says Mor. This differs from Oncotech's assay, says Sean McDonald, President and CEO of Precision Therapeutics, which 'is really built on exposure to very high doses of the drug.

'We're providing information across the entire dose range on what drugs a patient is likely to be sensitive to and not just drug resistance.,' says McDonald. 'It's more informative to the clinician.' The study also incorporates some genetic measures of response.

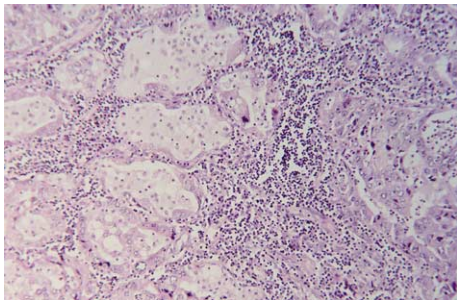
References

1 Flick, M.B. *et al.* (2004) Apoptosis-based evaluation of chemosensitivity in ovarian cancer patients. *J. Soc. Gynecol. Invest.* 11, 252–259
2 Kamsteeg, M. *et al.* (2003) Phenoxodiol – an isoflavone analog – induces apoptosis in chemoresistant ovarian cancer cells. *Oncogene* 22, 2611–2620

Gefitinib does not increase survival in lung cancer patients

Roy M. Golsteyn, roy.golsteyn@fr.netgrs.com

On 17th December 2004, the FDA released a statement that patients treated with Gefitinib (Iressa) did not show clinical benefit when compared with those treated with a placebo. Based upon this information, the FDA is considering whether or not to withdraw Gefitinib from the US market.



Responder genotypes

Gefitinib is a small molecule inhibitor of the Epidermal Growth Factor Receptor kinase (EGFR) developed by AstraZeneca. It attracted the attention of the business, medical and scientific communities because it was the first protein kinase inhibitor approved for use in the treatment of non-small cell lung cancer (NSCLC). Lung cancer, and solid tumours in general, are notoriously difficult to cure, therefore, the news that a targeted approach might be effective was well received by all participants in the fight against cancer. Gefitinib showed remarkable activity to shrink NSCLC tumours in approximately 10% of USA patients and 28% in Japanese patients when used alone. Analysis of the genotype of responders revealed that they carry activating mutations within the EGFR gene, an observation that reinforced the rationale for using Gefitinib.

Failure

The failure of Gefitinib to show clinical benefit amongst 1,692 patients in the ISEL phase III trial has raised several difficult questions about drug development. One would like to know why the ability of Gefitinib to shrink tumours in certain individuals could not be translated into an increase in survival in a population of patients. Despite the fact that no overall improvement in population survival could be measured, an increase in survival was detected in a small subgroup of non-smoking and oriental patients, which was consistent with data from previous studies. The results from the Gefitinib study contrast with those of a second EGFR inhibitor, Tarceva, developed jointly by OSI, Roche and Genentech. Tarceva showed clinical benefit in a placebo-controlled Phase III trial in patients with NSCLC. Although it must be reassuring to patients and to industry that a targeted compound is clinically active in a difficult disease setting, the factors that led to the success of one compound but not the other against the same target remain ambiguous.

Fast-track approval

During its development, the news stories about Gefitinib had cycled several times between good and bad. The FDA approved Gefitinib in 2003 in a fast-track system even though it had failed in a phase III combination trial, but in early 2004 the identification of patients likely to respond to Gefitinib in monotherapy had boosted interest in the compound. Before the FDA announced the results from ISEL trial, financial analysts were predicting $1 billion annual sales. Since the FDA announcement, AstraZeneca have withdrawn their application for market approval of Gefitinib in Europe, and they awaiting a decision on whether continue its use in the USA.

Lung cancer kills over 1 million patients a year, worldwide. Sadly, over 20 years of clinical trials with classical cytotoxic approaches have increased patient survival by only two months and so there is a desperate need for new treatments. Gefitinib was the first kinase inhibitor molecule to go against one of the most difficult human tumours, and it appears to be losing the battle. Yet, it is likely that there is still much to be learned about Gefitinib and protein kinase inhibitors in general because it has been used to treat over 200,000 patients up to the time of the FDA announcement. Hopefully, some of this information will help to identify better drugs for patients and lead to fewer failures for the pharmaceutical industry.

Hematopoiesis: cMyb enters centre stage

Treasa Creavin, t.creavin@elsevier.com

Researchers have made a significant advance towards understanding the production of blood cells in the body. Michael Cooke and colleagues from the Novartis Research Foundation (http://web.gnf.org/scientific/immunology/cooke.html) have identified a protein – cMyb – that is a key regulator of blood cell formation, or hematopoiesis. It also has an important role in controlling the number of hematopoietic stem cells (HSCs) – cells that are the common precursors of red and white blood cells and lymphocytes. Their discovery will pave the way for advances in adult stem-cell therapy.

1359-6446/04/$ – see front matter PII: S1359-6446(04)03401-X