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Strategies for the next generation of drugs

A political solution must be found to the increasing gap between treatment options and the economic resources needed to pay for them, delegates at the third Alpine meeting (Innsbruck, Austria, 14–16 March, 2007) of the Biotherapy Development Association (BDA) heard.

The non-profit BDA forum included government regulators, academics, representatives from the pharmaceutical industry and patient advocacy groups.

Professor Max E Scheulen (Universitätsklinikum Essen, Germany) said that while per capita healthcare spending in Europe is at its highest level ever, scarcity is being discussed more heatedly than at any other time. 'Increasingly, the acceleration of technical and pharmacological progress will lead to growing discrepancies between treatment options and economic resources,' he said.

Novel agents may, however, change the patterns of spending. Mr Paul Trueman (University of York Health Economics Forum, UK) said that targeted therapies 'can shift the economics from excessive end-of-life spending to investing in prevention, earlier diagnosis, and early treatment of chronic conditions.'

BDA Chair, Professor Heinz Zwierzina said that biomarkers for cancer needed to be found in order to reduce the number of patients who receive a particular drug. 'Therapies will be expensive if only 20% of those treated are likely to respond,' he said. While the new technology of proteomics will help scientists find the biomarkers, this development poses problems for industry. 'It narrows the potential market for them,' Professor Zwierzina said. 'However, it is the only solution to insufficient resources.'

A problem from industry's point of view, said Mr Chris Teale (AstraZeneca) is that 'innovative drugs are becoming more difficult to find and more expensive to develop'. Traditionally, drugs had to negotiate safety, efficacy and quality hurdles. Now, however, there are at least 3 additional hurdles: national pricing and reimbursement, local market access, and health technology assessment (HTA).

HTA is the most demanding condition, Mr Teale said, and nearly half of licensed therapies fail it in some way. Jumping these additional hurdles has profound implications for drug development, due to evidence, outcomes and epidemiological research being required in areas rarely explored in the past. This adds to the cost of development, but will ultimately improve patient access to valuable new medicines, lead to a more equitable distribution of limited healthcare funds, and allow appropriate pay-back for investment in innovation.

Professor Zwierzina said that an honest debate was called for. 'In the end, the politicians will decide how much money there is.' He noted that the UK's National Institute for Health and Clinical Excellence (NICE) has the most transparent system in Europe: 'On the other hand, it is also a rather restrictive system and patients in the UK are less likely to receive currently available innovative drugs compared to other Western countries.'

(*A forthcoming EJC supplement will provide a full report of the meeting*).

Virtual colonoscopy 'is safe and cost-effective'

Virtual colonoscopy – or CT colonography (CTC) – is the most cost-effective and safest screening option available, according to a US/Italian study (*Cancer 2007 doi:10.1002/cncr.22668*). Polyps greater than 5 mm only should be followed up with optical colonoscopy, they said.

The study modelled 100,000 people over 50 years old. It found that CTC with a 6mm threshold for follow-up cost US $4,361. With no threshold, it was US $7,138. This compares with $9,180 for optical colonoscopy and $7,407 with flexible sigmoidoscopy.

Targeting lesions of 5 mm or less is extremely expensive and results in a large proportion of adverse events, from abdominal pain to perforation of the colon and bleeding, the authors say. CTC uses x-rays and imaging software, and is better tolerated by patients, they said.

Current CTC guidelines recommend reporting polyps greater than 5 mm only. The authors said that almost half of the complications with optical colonoscopy were attributable to working up diminutive lesions.

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Undescended testis: 'Treat early'

Early treatment for undescended testis decreases the risk of testicular cancer, say Swedish researchers. Men who had been treated at 13 years or older had approximately twice the risk of developing the disease than those treated before the age of 13.

The study (*N Eng J Med 2007;***356**: 1835–41) included 16.983 men who were surgically treated for undescended testis, as recorded on the comprehensive Swedish Hospital Discharge Register. They were followed from 1965 to 2000 through linkage to the Swedish Cancer Registry and a Population Register – a total follow-up of 209,984 person-years. Within the group, 56 cases of testicular cancer were identified.

Those who were treated before they were 13 had a relative risk of developing testicular cancer of 2.23, compared with the Swedish general population. Those treated later had a relative risk of 5.4.

Since risk was increased in the entire cohort, the study is partly consistent with the hypothesis that the risk of germ-cell cancer of the testis is largely determined in utero. However, the results also suggest that 'puberty, here defined arbitrarily as beginning at the age of 13 years, is another crucial event in testicular carcinogenesis'.

Unambiguous recommendations for early treatment exist, yet 'a proportion of boys with cryptorchidism are still left untreated until much later in life', the report states. In Sweden in 2005, about 6% of orchiopexies were performed at the age of 13 or older. In the UK and the Netherlands, in the late 1990s, it was 10–20%.

'Given the relative risk in our study, we calculated that 69 boys would need to be treated before 13 years of age (instead of at or after that age) to avoid one case of testicular cancer in Sweden before the age of 55 years,' the authors conclude.

New markers to detect prostate cancer

Aberrant methylation in cells obtained after prostatic massage could detect localised prostate cancer, suggests a new study (*Clin Cancer Res* 2007;**13:** 1720–25). The researchers have proposed a set of genes that could be used on the basis of their methylation status to stratify patients into high-risk or low-risk groups for development of prostate cancer.

Author Morgan Rouprêt (Institute for Cancer Studies, University of Sheffield, UK) says, 'as [prostate-specific antigen (PSA)] is not prostate-cancer specific, there is a lack of [a] specific biomarker to help clinicians in detecting new cases of prostate cancer. Thus, there is a growing interest in [the] medical community for new reliable markers, and we believe that these specific genes could be of interest [for] prostate cancer management'.

The researchers obtained urine samples from 95 patients with localised prostate cancer who underwent radical prostatectomy and from 38 matched controls. The patients underwent prostatic massage by digital rectal examination in the operating room to obtain prostate secretion at the external urethral meatus. The first voided urine after this process was used to extract DNA for methylation analysis, and ten genes were analysed for aberrant methylation by use of quantitative real-time methylation-specific PCR.

'THESE SPECIFIC GENES COULD BE OF INTEREST FOR PROSTATE CANCER MANAGEMENT'

By use of such analysis, 88 of 95 patients with early prostate cancer were diagnosed successfully (sensitivity=0·93). 93% of patients with cancer showed hypermethylation of at least one gene. Except for P14 and P16, methylation of all genes was significantly more frequent in patients with cancer than in controls ($p<0·05$). Four genes (*GSTP1*, *RASSF1á*, *APC*, and *RARB2*) showed the greatest statistical difference in aberrant methylation between patients with prostate cancer and controls. This four-gene panel discriminated malignant cells from non-malignant cells very well (sensitivity=86%, accuracy=89%).

Yair Lotan (University of Texas Southwestern Medical Centre, Dallas, TX, USA) believes that the small sample size is a potential limiting factor of this study, and suggests that the test needs to be assessed in many more patients.

'The current screening of prostate cancer using PSA has low specificity resulting in many unnecessary biopsies. If this test is validated in a larger cohort and found to be both reproducible and cost-effective, it may reduce the number of these unnecessary biopsies by determining which patients are at higher risk for prostate cancer', he adds.

Sharan Prakash Sharma

*This story originally appeared in Lancet Oncol 2007;***8**:380.

Organisations unite to beat cervical cancer

The International Union Against Cancer (UICC) and the European Cervical Cancer Association (ECCA) have joined forces in their work against cervical cancer in Europe.

The new alliance will mean mutual exchange of memberships and the cross appointment of advisors to help ensure that cervical cancer prevention programmes are effectively integrated to maximise their impact in Europe.

ECCA President, Imelda Read welcomed the increased level of cooperation. 'Ultimately our close cooperation will help to increase the impact of our programmes and lead to further decreases in cervical cancer rates in Europe.'

Guidance on end of life

The British Medical Association (BMA) has issued updated guidance on withholding and withdrawing life-prolonging treatment. It was prompted by the Mental Capacity Act, 2007.

The guidance covers issues such as how to assess capacity and the patient's best interests, providing basic care, decision-making on behalf of adults, young people, children and babies, and by those who have made an advance decision about medical treatment.

The Act gives patients the right to nominate a welfare attorney to act on their behalf when they can no longer communicate their wishes to health professionals. Where a patient lacks capacity and has no family or friends, an independent mental capacity advocate has to be involved in serious medical decisions. The Act also puts advance decisions about medical treatment onto a statutory footing for the first time in England and Wales.

Dr. Tony Calland, Chair of the BMA's Ethics Committee, said he welcomed the legislation, which provides formal mechanisms for patients' wishes – for example, about the stage at which active treatment aimed at prolonging their life should be stopped – to be heard: 'The primary goal of medicine is to benefit patients and if medical treatment can no longer do this then, ethically and legally, doctors must consider whether it should be withdrawn.

'The BMA does not support blanket rules regarding decisions to withdraw or withhold treatment. Each patient, irrespective of their age and illness, should be treated individually.'

The BMA guidance can be found at http://www.bma.org.uk

'Triple negative' cancers linked to disadvantage

Aggressive breast cancers which lack significant tumour markers are most common among young, poor, minority women, say US researchers. The so-called 'triple negative' cancers have no receptors for oestrogen (ER), progesterone (PR) or human epidermal growth factor 2 (HER2).

Approximately 15% of breast cancers are 'triple negative' and considered to be basal-like subtypes. Hormone adjuvant therapy is less likely to be effective and the tumours are associated with poor prognosis and survival. They are most often found in African American women but little is known about other risk factors.

The researchers, from the Public Health Institute in Sacramento, California, compared the demographics, clinical characteristics and survival rates of 6,370 women with triple negative breast cancer, with those of 44,704 women with other breast cancers.

Race and age, as well as socioeconomic status, were risk factors for this type of breast cancer. African American women were at greatest risk, followed by Hispanic women. The tumours were more aggressive than other breast cancers, diagnosed at a later stage and associated with shorter survival, regardless of the stage at diagnosis. African-American women had the poorest 5-year survival, and only 14% were alive 5 years after diagnosis.

Capecitabine approved for gastric cancer

The European Commission has approved capecitabine (Xeloda) in combination with platinum-based chemotherapy for first-line use in patients with advanced stomach cancer. This follows the drug's approval for use as a first-line monotherapy in metastatic colorectal cancer and as an adjuvant treatment for colon cancer.

Capecitabine is given orally and, according to manufacturer Roche, reduces the time patients need to spend in hospital by 80%.

The approval was based on the phase III trials ML17032 and REAL 2. Both showed that overall survival among patients in the arms including capecitabine was at least as long as among those receiving intravenous 5-fluorouracil (5-FU).

Clinical trials in the elderly

Age is a barrier that can be overcome in clinical trials, according to a Canadian oncologist. The concept of randomised controlled trials in older patients with cancer 'is a reality that has come of age,' she writes (*N Eng J Med 2007;***356***:1575–6*).

Dr. Lillian Siu (University of Toronto, Canada) says that many physicians and patients have an innate bias that associates older age with inferior outcomes: 'Ageism is probably the greatest impediment to the enrolment of older patients in trials for cancer therapy.'

Dr. Siu was commenting on a French trial of radiotherapy for glioblastoma in patients more than 70 years old randomised to receive supportive care with or without radiotherapy (*N Eng J Med 2007;***356***:1527–35*).

The trial was halted early at the first interim analysis because the difference in survival between the 2 treatment groups was greater than the preset boundary of efficacy. Improvements in survival were modest (a median of 29.1 weeks in the radiotherapy group, compared with 16.9 weeks among those receiving supportive care alone). This, the authors say, is about half the survival gain reported in earlier studies in younger patients.

However, health-related quality of life was similar between the 2 groups, before and after treatment. Furthermore, there was no reduction in cognition among elderly patients.

The French researchers said that likely causes for the under-representation of elderly cancer patients in clinical trials include study-imposed restrictions, coexisting conditions, concern about the toxic effects of treatment, patient and family preferences, and the reluctance of physicians to enrol elderly patients in clinical trials.

'Nevertheless, our study shows that these barriers may be overcome, even in trials that involve a rapidly progressive, fatal disease, such as glioblastoma, and a palliative-care comparison group,' they say.

Cetuximab 'improves overall survival'

Cetuximab (Erbitux), a monoclonal antibody which targets the epidermal growth factor receptor (EGFR), significantly improved overall survival in patients with advanced colorectal cancer, according to a study reported at the 2007 Annual Meeting of the American Association for Cancer Research (*14–18 April, 2007; Los Angeles, USA*).

The CO.17 trial included 572 patients with advanced colorectal cancer whose disease was no longer responding to chemotherapy. All patients had tumours with detectable EGFR. They were randomised to receive best supportive care, with or without cetuximab.

Results showed a statistically significant 23% improvement in overall survival (the primary outcome). The median survival was 6.1 months in the cetuximab group compared to 4.6 months with best supportive care alone. There was a 32% reduction in the risk of disease progression.

Professor Derek Jonker (University of Ottawa, Canada), co-chair of the study, said: 'This is the first time a single agent biologically targeted therapy has demonstrated a survival advantage in patients with colorectal cancer.' (*Proc AACR Annual Meeting 2007, Late Breaking Abstract #1*).

A second phase III trial showed that a combination of cetuximab and irinotecan significantly improved progression free survival compared to irinotecan alone when used as second-line treatment (*Proc AACR Annual Meeting 2007, Late Breaking Abstract #2*).

The study randomised 1,298 patients with EGFR-expressing metastatic colorectal cancer who had failed oxaliplatin and a fluoropyrimidine. Patients receiving the cetuximab/irinotecan combination had significantly longer median progression free survival and significantly higher tumour response rate than those receiving irinotecan alone. Disease control was achieved in significantly more patients, but there was no difference in overall survival.

'Long-term protection' with HPV vaccines

Follow-up studies with a vaccine against the human papillomavirus found long-term protection against precancerous lesions of the cervix (*Proc AACR Annual Meeting 2007, Abstract #4900*).

A vaccine against HPV types 16 and 18 (Cervarix, GlaxoSmithKline) showed 100% efficacy in preventing precancerous lesions due to these virus types for up to 5.5 years. The initial study was a double-blind, controlled trial of 1113 women (aged 15–25 years) randomised to receive three doses of the vaccine or placebo; 776 women were followed for up to 67 months.

The vaccine induced a strong immune response in virtually all women, which was sustained for 5.5 years for both HPV types 16 and 18. At the end of the follow-up period, the average level of antibodies against both virus types was 11 times higher than those associated with natural infection.

Results showed 68% efficacy against precancerous lesions (CIN2+) and 38% efficacy against abnormal Pap smears, regardless of the type of virus detected. The vaccine provided significant protection against genetically similar viruses, with 88% efficacy against HPV 45 and 54% against HPV 31.

Professor Stanley Gall (University of Louisville, Kentucky, USA), said: 'These new data demonstrate the longest duration of protection seen in any cervical cancer vaccine trial reported to date.'

Second cancers among childhood survivors

Analysis of data from 13 registries in Europe, Iceland, Australia, Canada, and Singapore, confirmed that survivors of childhood leukaemia and lymphoma have a higher-than-average risk of developing a different type of cancer in later life (*Proc AACR Annual Meeting 2007, Abstract #3395*).

The registries collected data for at least 25 years over time periods between 1943 and 2000. Each provided individual data on leukaemia, Hodgkin's lymphoma, and non-Hodgkin's lymphoma, along with second cancers – new primaries, not recurrences or metastases – in children from infancy through to age 14. The cumulative incidence of second cancers was 2.43% within 30 years of having leukaemia, 12.7% after Hodgkin's lymphoma, and 2.5% after non-Hodgkin's lymphoma.

Dr. Paolo Boffetta (International Agency for Research on Cancer, Lyons, France), noted the high risk among Hodgkin's lymphoma survivors: 'This is probably due to the better survival of Hodgkin's lymphoma patients who received highly toxic chemotherapy, compared to other groups of patients'.

Erythropoietic agent 'decreased survival'

Darbepoetin alfa (Aranesp) was associated with decreased overall survival in patients with active cancer not being treated with chemotherapy or radiotherapy, according to results from a phase III trial (*Proc AACR Annual Meeting 2007, Late Breaking Abstract #3*).

The study randomised 985 patients with active cancer, and no chemotherapy or radiotherapy within 4 weeks of screening, to darbepoetin alfa or placebo. The most common cancers were non-small cell lung, breast and prostate cancer.

The number of transfusions was lower in the active treatment group but this was not statistically significant. The adverse event rate was similar but the overall number of deaths was significantly higher with active treatment (136 deaths vs 94 deaths with placebo; p=0.006). This difference in survival remained during post-hoc analysis adjusting for a range of factors, including stage of disease, prior chemotherapy and radiotherapy.

Professor John Glaspy (University of California, Los Angeles, USA), said: 'For now, we have to conclude that these agents may reduce survival in patients not on chemotherapy.'

Susan Mayor's attendance at the meeting was sponsored by Merck KGaA.

PODIUM

US research at a crossroad

Professor V Craig Jordan (Fox Chase Cancer Center, Philadelphia, USA), the 'father of tamoxifen', has studied the drug since the 1970s, when it was dismissed as a failed contraceptive. His work established tamoxifen as a treatment and preventive agent for breast cancer. Trained initially in Britain, he has worked for many years in the USA and is currently concerned about the funding of cancer research.

Surely the US has an effective funding system?
We have had a huge infusion of money for biomedical research over the past 20 years. It has increased the biomedical research community, and created a massive amount of new knowledge. We have had a clear cut agenda, with training programmes for the brightest and best, and exciting research programmes. The US has been the driving force in investigator initiated research: we could find the money for bright people to develop their good ideas.

What has changed?
The research agenda in the US has changed because there are insufficient funds. Fewer scientists are being adequately funded. Young scientists are not being supported and clinical trials are being cut back. This hasn't happened before. There has been a move to 'big science' rather than the individual breakthrough. One is the human cancer genome project, which is a great idea, but still, only an idea. The assumption is that when we get the information, we'll be able to fix cancer. But we may not be able to if we find 300 things are wrong.

Is 'big science' necessarily a bad thing?
To take an analogy: imagine highly trained and well-prepared soldiers sent to finish off a war. They have arrived successfully and are making good progress. Without warning, the powers that be withdraw all resources. The soldiers are given no more petrol, no more ammunition, supplies or replacements and told just to get on and do the job. Meanwhile, back at headquarters, money is poured into thinking about the reasons why wars happen and how they can be avoided, and developing weapons that will be needed 50 years from now.

By focusing on the big science projects, we are in effect telling people who have cancer now to come back for help in 50 years' time. The lack of resources also robs young investigators of the chance to follow up their ideas.

How restricted are funds?
Young people are not able to get the grants they need to get started. Big institutions and philanthropy are expected to pay them until they are sufficiently well-established to get federal funding. But there is no commitment from the top for early career development.

You're saying this change is a gamble?
Knowledge is power, and will bring insights. But information from clinical trials is also useful to save lives. The human cancer genome project will be like having a map of America, which tells you where cities are but gives no idea of what is going on in each. To figure that out, we need a cadre of bright, well-trained individuals to take over the next generation.

Big science and technology is the goal and clinical trials are seen as a distraction. This may not necessarily pay off big dividends over the long term.

Is there any protection for clinical trials?
The pharmaceutical industry with its product-defined goals seems to be mandated to control clinical trials. But if pharmaceutical companies are the only ones undertaking clinical research, there will not be free access to information. Confidentiality issues will prevent us appraising all the data and seeing the whole picture. Pharmaceutical companies do not necessarily share the same aims as healthcare providers; and also do not have the clinical trials mechanism which has been build up since the 1960s in the public sector. It will disappear without long term commitment.

What about laboratory work?
Industry's expertise lies in developing drugs, not finding targets. The initial work is done by smart young people in universities. Our foundation of basic and translational knowledge is quite rightly government-funded and the role of the pharmaceutical industry is to test and market products with an emphasis on safety. There is no return on an investment in basic knowledge for a company. There must be a product.

Does the new system have any redeeming features?
Sincere individuals are trying to make the best out of a bad system and truly believe that they will help humankind in the long term. But there are too few resources and our scientific infrastructure is being dismantled. Only one in ten researchers will be funded with half the money they need to do the research. I am concerned that one or two generations will disappear in the meantime – patients and researchers. If we lose too many young researchers, we lose brains, integrity, and the ability to figure things out. Everything is being pushed on to shoulders of philanthropists, not government, and there doesn't seem to be any safety net to ensure continuity and progress.