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NEWS...NEWS...NEWS

Report highlights European inequalities in access to cancer drugs

Cancer patients across Europe do not have equal access to innovative cancer drugs, and the speed at which they benefit depends upon the country in which they live, concluded a report launched at the European Parliament in October.

The study conducted by Karolinska Institutet and Stockholm School of Economics, names Austria, Spain and Switzerland as the most advanced countries in terms of early adoption and availability of new drugs, while demonstrating the UK, Czech Republic, Hungary, Norway and Poland lag far behind.

In the study Drs Nils Wilking and Bengt Jönsson surveyed the total sales of 56 oncology products in 19 countries in Europe accounting for 447 million people, or 76% of the total population in Europe (excluding Russia and Turkey). They looked at how the composition of cancer drugs used in each country varied between those introduced before 1993 and those after 1998. ''This report illustrates the inequities in access to cancer drugs in Europe. We believe these inequities cannot be allowed to persist,'' wrote Drs Wilking and Jönsson. ''It is our hope that this report will inspire and motivate policy and decision makers to act immediately to address these inequalities for the benefit of all cancer patients.''

Cancer health care costs, said the authors, are not sufficient to cover the burden of the disease. In 2004, 1.7 million Europeans died from cancer, yet the total healthcare cost for cancer in the countries included in the report was estimated at €54 billion, or €120 per inhabitant, which represents only 5% of total health care expenditure. Costs associated with inpatient hospital care dominate the direct costs of cancer in Europe, accounting for 60–94% of all costs, while less than 10% is spent on drugs.

In the report Dr Frank Lichtenberg of Columbia University also highlighted how better access to more innovative cancer drugs brings survival benefits to patients. His analysis of the situation in the USA demonstrated that the increase in the stock of cancer drugs accounted for 50–60% of the increase in survival rates in the first 6 years post diagnosis.

Nowhere in Europe, says the report, is the decisive role played by economic evaluations more evident than in the UK, where the National Institute for Health and Clinical Excellence (NICE) issues guidance. While a positive NICE review should lead to more rapid and wider access to new treatments, there are issues about NICE's capacity to cope with the increasing workload of such evaluations. It can take up to 18 months for a product to be referred to NICE and then the timeline of a NICE review is 62 weeks. The consequences of such delays are clearly demonstrated by adverse comparisons between the UK and other European countries studied in the report. The issue was highlighted in the UK in the same week as the report's publication when Health Secretary Patricia Hewitt, bowed to pressure and announced that all women diagnosed with early stage breast cancer would be tested for suitability for treatment with Herceptin.

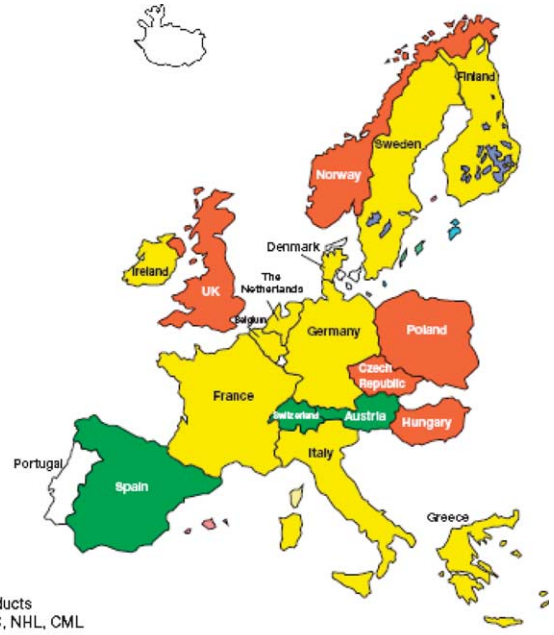
The authors conclude that centralized procedures need to be introduced in Europe to evaluate the benefits of each drug soon after marketing authorization. ''It's not necessarily the case that a high uptakes of different drugs is a good thing, but having a more uniform approach would stop patients having to travel round Europe for treatment,'' said Dr Wilking.

Further recommendations include:

- Ensuring drugs are available at the national level within 180 days of EU authorization.
- Ensuring economic evaluations and health technology assessments, such as those done by NICE, are done quickly.
- Ensuring funding for new drugs is available on a proactive rather than reactive basis.

Source: 'A pan-European comparison regarding patient access to cancer drugs' by Nils Wilking and Bengt Jönsson, Karolinska Institutet in collaboration with Stockholm School of Economics Stockholm, Sweden.

The report can be downloaded from the Karolinska Institutet site.
http://info.ki.se/article en.html?ID=4540



Summary uptake of new oncology products in breast and colorectal cancer, NSCLC, NHL, CML and bone metastases

- Above average
- Average
- Below average
- Data not available/analysed

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Cervical cancer vaccine 100% effective

A trial presented at *Infectious Diseases Society of America (IDSA)* annual meeting (October 6–9) in San Francisco raises hope that vaccination for cervical cancer could become available within the year.

Results from the Future II study , presented by Finn Egil Skjeldestad from SINTEF Health Research, Norway, showed that the vaccine, Gardasil ™ (a quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine), given in three doses over six months was 100% successful.

In the phase III study 12,167 women aged between 16 and 23 years were randomised to vaccine or placebo given at day 1, months 2 and 6. Pap tests and HPV swabs were taken at day 1, and months 7, 12, 24, 36 and 48. The study then evaluated incidence of HPV 16/18-related cervical intraepithelial neoplasia (CIN) 2/3 and non-invasive cancers from pap tests and HPV swabs taken at day 1, and months 7, 12, 24 36 and 48.

Results reveal no cases of CIN2/3 AIS were observed in the vaccine group (n = 5301), compared to 21 in the placebo group (n = 5258) (p = <0.001). A second analysis was performed to include women who developed HPV infections during the vaccination program and those who missed follow-up appointments.

The researchers found that the vaccine was 97% effective after even one dose. Only 1 out of 5736 vaccinated women developed a cervical lesion, compared to 36 out of 5766 women in the placebo group.

None of the women involved in the trial were forced to pull out as a result of adverse side-affects. The most serious adverse side-effect reported was local discomfort at the injection site.

David Luesley, who holds the chair in Gynaecological Oncology at the University of Birmingham, commented: ''This is a landmark study, that has been adequately powered to provide robust evidence that a vaccination programme can stop cancer. It offers an excellent example of how good basic virology and immunology research can be used to develop highly effective health care interventions.''

But, he added, there are still unanswered questions, such as how often the vaccine would need to be given, how early the vaccine should be given and what happens if women who have already been exposed to HPV are vaccinated?

He questioned the enthusiasm of health departments to embrace vaccination programmes. ''Since they cannot ignore the women who have already been exposed to HPV they will have to run vaccination programmes in tandem with screening for many years to come and that will lead to additional expense.''

Gardasil™ was designed to target HPV types 16 and 18, which account for 70% of cervical cancers, and HPV types 6 and 11, which account for 90% of cases of genital warts. These four types 6, 11, 16 & 18 also cause a significant proportion of low grade cervical lesions that result in ''abnormal'' Pap smears. Merck's official reason for including the warts strains is that they can confuse screening tests, leading to unnecessary scares.

''An important feature of including HPV types 6 and 11 is that by conferring protection against male genital warts this might provide an incentive for men to be vaccinated, with the knock on effect that they would might no longer transmit the cancer-causing strains to women,'' said Professor Luesley.

The success of the trial focuses attention on ethical concerns, such as whether the cost of delivering preventative drugs could make them inaccessible to developing nations, and the challenge of convincing families from traditional cultures to vaccinate their daughters against sexually transmitted viruses. In the US, for instance, some religious groups are reported to be gearing up to oppose vaccination.

Merck remain on track to submit a Biologics License Application for Gardasil to the American Food and Drug Administration (FDA) in the fourth quarter of 2005, shortly followed by the submission by Sanofi Pasteur MSD of a Marketing Authorisation Application to the European Medicines Agency (EMEA).

Devising strategies to reduce diagnostic error

US investigators found cancer diagnosis errors occur in up to 11.8% of all reviewed samples in a study comparing cytological and histological specimens. Following patient records the study, published in *Cancer* (October 10 online), went on to show 45% of gynaecological errors and 39% of non-gynaecological errors were associated with patient harm.

The report, led by Dr Stephen Raab from University of Pittsburgh School of Medicine, examined cancer diagnosis data from 4 unnamed institutions from the Mid-Atlantic and Midwest region of the USA. A ''review'' pathologist selected cases in which cytologic and surgical specimen pairs showed discrepancies, for example, the results of Pap tests and cervical biopsy being different or lung brushing and biopsy being different. An interpretation error was defined as an error in disease categorization that could be further classified as an overcall (if the review diagnosis was categorically lower than the original diagnosis) or an undercall (if the review diagnosis was higher than the original diagnosis). A sampling error was defined as an error in which the diagnostic material was not present on the slide. Medical records were then reviewed to determine patient outcomes.

''The concept of standards just doesn't exist yet,'' said Dr Raab. ''So, there are no really good ways to evaluate and compare the quality of testing and no standard for the measuring of harm as a result of error. Clearly, there's enormous differences between institutions and we have to figure out why.''

The study, he added, represents the first step in decreasing national inter observer diagnostic variability. In the second phase, the team are analyzing the cause of the error to devise reduction plans that can be implemented in all laboratories. ''The entire pathology community will need to take a role in this effort,'' concluded Dr Rabb.

Patients use complementary and alternative medicines

Almost half of patients with cancer who receive chemotherapy and radiotherapy are using at least one type of complementary and alternative medicine (CAM). However, about 75% of patients do not tell their doctor, according to research at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (Oct. 16, 2005; Denver, CO, USA). Author Neha Vapiwala (University of Pennsylvania, PA, USA) explains: ''An obvious component is failure of many physicians to ask their patients about CAM use during conventional therapy. Alternatively, physicians may verbally dismiss CAM use and openly express distrust of it to their patients. While some patients may discontinue or avoid CAM as a result, others may continue to use it secretly, for fear of angering or antagonizing their doctors''. Susie Wilkinson, Marie Curie Palliative Care Research Institute, London, UK, agrees with the findings: ''There is a lack of communication between patients and doctors over the use of CAM. Patients often feel that their doctors will not be interested in hearing about CAM''. Helen Gunson, Bristol Cancer Help Centre, Bristol, UK, adds: ''Clearly, it is extremely important that doctors and health professionals are aware of their patients' use of CAM, particularly when it comes to use of herbal medicines and supplements where there may be interactions with conventional treatment''. The potential for adverse interactions between CAM and conventional treatment is also a concern for Vapiwala, who said that few controlled, clinical studies of CAM use have been done in patients with cancer.

Cathel Kerr

This story originally appeared in Lancet Oncol

Cancer consensus needed on transplant immunosuppression

Switching immunosuppressive regimens significantly reduces the risk of renal transplant patients developing cancer, reports a phase III prospective study presented at 12th Congress of the European Society for Organ Transplantation, 15–19 October, Geneva, Switzerland.

In the oral presentation (OR-205) 430 transplant patients were randomized 3 months post transplant to either continue to receive a combination of sirolimus (SRL) and cyclosporine (CsA), or have their CsA withdrawn and receive ongoing SRL. The 5 year data, presented by Dr Joseph Campistol from the Nephrology Department at the University of Barcelona, Spain, showed that 19 of the SRL and CsA population had developed non skin malignancies (including cancers of the lung, oropharynx, kidney, GI, prostate, breast, thyroid and cervix); compared to just 7 of the SRL patients ($p = 0.015$).

In addition, at 4 years graft survival was significantly better for patients who had CsA withdrawn and remained on a maintenance regimen of SRL, compared with those maintained on CsA ($p = 0.024$).

''This is the first prospective study with long term follow up showing withdrawing CsA leads to a reduced tumour incidence, without any adverse effects on rejection,'' said Dr Campistol. ''Drug selection has important implications for both patient quality of life and survival.''

An additional study just published in Transplantation (26th October), adds further weight to these findings. The retrospective analysis of more than 33,000 renal transplant patients on the Organ Procurement and Transplant Network for Organ Sharing (OPTN/UNOS) database, who received organs between 1996 and 2001, by Dr Myron Kauffman, from UNOS, showed that 0.6% of patients treated with m TOR inhibitors (SRL and everolimus) developed new cancers, compared to 1.81% receiving calcineurin inhibitors (CsA, tacrolimus) ($p < 0.001$).

Animal evidence, said Dr Campistol, exists to support the withdrawal of CsA. Calcineurin inhibitors have been shown to increase transforming growth factor-B (TGF-B) expression that is associated with cellular changes characteristic of invasiveness, while M TOR inhibitors reduce TGF-B and vascular endothelial growth factor (VEGF) expression and inhibit tumour angiogenesis.

''A consensus conference is now needed to consider management of transplant patients both with current cancer and a past history of cancer,'' said Dr Campistol ''In addition, guidelines are needed to ensure all patients on transplant waiting lists are screened for cancer.''

Breast cancer advances

New survival predictions released by Cancer Research UK in October offer good news for breast cancer patients. Almost two thirds (64%) of women diagnosed with beast cancer between 2001 and 2003 are likely to survive for at least 20 years, and 72% are likely to survive for 10 years. And for women diagnosed between the ages of 50 and 69, survival is even better, with 10 year survival estimated at 80% and 20-year survival at 72%.

The findings are based on a study by Michel Coleman, professor of epidemiology and vital statistics at the London School of Hygiene and Tropical Medicine, using data from the National Cancer Registry at the Office for National Statistic on women diagnosed with breast cancer in England and Wales between 1971 and 2003.

In comparison with even a decade ago, said Professor Coleman, improvements are dramatic. In the early 1990s only 54% of sufferers could expect to live for 10 years and only 44% for 20 years. Survival advances are based on earlier detection through the national screening programme, new drugs such as aromatase inhibitors and the introduction of specialist treatment through multi disciplinary teams. In practice, these estimates are likely to be conservative since they do not include the impact of recent advances in therapy.

First for Oral Mucositis

Palifermin (Kepivance®) is the first product to receive European Union (EU) regulatory approval to decrease severity of oral mucositis in patients with hematologic cancers undergoing myeloablative therapy and requiring autologous blood and bone marrow transplants. Approval is based on a phase 3 double-blind study comparing palifermin with placebo in 212 patients with hematologic malignancies. Results show the incidence of grade 4 oral mucositis was 20% in patients randomized to palifermin (60 micro-g/kg/day), compared to 62% with placebo.

EUROFILE

7th framework: funding hopes dashed

Early hopes of a massive increase in funding under the next 7th Framework research programme (FP7) have been dashed already, provoking angry responses from the officials involved in drafting it. The 'Lisbon agenda' which aims to bring European competitiveness levels up to those of the USA, was the main driving force behind the large budget originally proposed – an increase from nearly €18bn to €73bn. The Commission and member states are continuing to press ahead with planning for an FP7 programme at this level of funding, but everyone knows that the final budget will be much less.

The draft plan for FP7, including funding, is currently before the Council of Ministers, and the first reading in the Parliament is expected in December. Disagreements between member states have already put FP7's future in jeopardy. A compromise from the Luxembourg Presidency, which reduced the budget to €43bn, was received without much comment, which would seem to indicate that funding may be substantially reduced without any protest from political circles.

Most people assume that Commission officials and member states are waiting to see what the final budget will be so that they can decide where to make cuts. ''But there is no Plan B,'' said Octavi Quintana Trias, head of health at DG Research, speaking to an audience of policymakers at the European Health Forum, Gastein, Austria in October. ''To say that there is would be to admit that we are willing to negotiate, and we are not. The major problem in European science is under-resources, and unless we address this Europe will have very severe problems and the situation will become extremely serious in as little as 5–10 years.''

''It is a major challenge for politicians'', he continued. ''It's not just a matter of a 5–10% increase, but a substantial increase is needed. Fragmentation of research is another area where comparison with the US is dramatic. The US funds science from one single pot, which means that it is more efficient and effective. In Europe public funds for research are scattered throughout national and regional programmes.''

Only a strong and united pan-European research effort could save the continent from economic decline, he said. But the funding required for such an effort looks increasingly unlikely to be forthcoming, and even the much-vaunted European Research Council (ERC) now looks in danger. On 18 July the Commission announced the appointment of the first scientific council for the ERC, but what will happen to it if member states cannot reach agreement on its budget?

Speaking to the European Parliament's industry, research, and energy committee in September, Research Commissioner Janez Potocnik told MEPs that the ERC was 'here to stay', however deep the cuts imposed on FP7. ''I can calm worries about this affecting the ERC,'' he said, but would not be drawn over the size of the budget likely to be allocated to it. The Luxembourg compromise, he said, ''was the most worrying fact because it shows the state of mind in the member states.'' The compromise would mean a 40.9% cut in the FP7 budget, he added. ''If this were to happen in practice, there would be a lot of serious questions raised about how to go on with the work on the Framework Programme.''

The committee will delay giving its opinion on FP7 until the budget is agreed. Once this has happened, Polish MEP and rapporteur Jerzy Buzek will produce a report and have the committee vote on it within 2 months.

While member states argue, the Commission is getting restless. Multinational companies are increasingly choosing to invest in countries where outlay in science is high, such as China. ''We must heed this wake-up call'' said Janez Potocnik.

''FP7 is an essential part of the revival of science in the EU,'' said Quintana Trias. If substantial budget cuts are imposed, he added, the commission may have to limit research topics covered by the European Research Council, for example, and advertise projects once every 2 or 3 years instead of annually.

But even within the European Parliament, a strong supporter to date of the proposed budget increase, there is dissent on how it should be spent. The development committee has issued a report asking for the commission to spend more FP7 money on research into diseases affecting the developing world, such as HIV/AIDS, TB, and malaria. The industry, research, and energy committee wants more money – a minimum of €300m – spent on renewable energy and €200m on energy efficiency.

With such vested interests involved, one wonders whether there will ever be agreement either on the budget or content of FP7. However, with so many voices raised in alarm at the possibility of missing the last chance to make Europe really competitive in science, not just in relation to the US but also with the emerging Asian economies, maybe there will be a happy ending. An agreement could be reached under the UK Presidency, which runs to the end of this year, or brokered by the Austrians who follow. Left later than that and the boat will have been well and truly lost, say both scientists and the Commission.

Mary Rice
Brussels

PODIUM

Championing a forgotten tribe

In October Professor Tim Eden took up the UK's first professorial chair in Teenage and Young Adult Cancer at The University of Manchester, with clinical duties at the Christie, Central Manchester and Manchester Children's University Hospitals NHS Trusts The chair has been funded by a grant of £2.5 million from the UK Teenage Cancer Trust. Here Professor Eden, who trained initially as a paediatrician and then moved into paediatric haematology and oncology, outlines his vision for teenagers with cancer.

Professor Tim Eden

1. How widespread are teenage cancers?

From cancer registry data tumours in teenagers and young adults appear to be on the increase, rising by about 1% per year. Cancer accounts for 11% of all deaths of teenagers and young adults, representing the most common cause of non-accidental death in this age group.

2. Why was there a need to fund a chair in teenage cancer?

In many ways teenagers with cancer are a forgotten tribe because unlike children and older adults there are no automatic clinical routes for referral. They tend to be treated by different clinicians, with the result nobody has a really good handle on their tumours and treatment. When we looked at survival we found that, unlike other age groups, there had been much less improvements over the last 20 years. Also, the number of teenagers entering clinical trials remains low. The lack of research means we still do not understand why teenagers and young adults get cancer. They lack exposure to known carcinogens and have a different spectrum of tumours from children and older adults.

3. Could you outline the responsibilities of your post?

Essentially my remit is to provide a national research lead and voice on teenage cancer. The aim is to advance understanding of the diseases, improve treatment and produce better psychological and emotional support. I am particularly looking to increase research and improve clinical trial opportunities. This must be a collaborative process, working with colleagues in the UK and internationally. In addition I'll continue to deliver patient care.

4. What collaboration is needed between adult and paediatric physicians?

One of the most important aspects in teenage cancer is to develop good collaboration between adult and paediatric physicians to find the most appropriate professional to treat each case. If a young person has a childhood type of leukaemia there is good evidence that they do better on a children's protocol. Conversely, if they have a melanoma, carcinoma of the breast or bowel, then an adult oncologist would be more appropriate. It is all about working together to optimise treatment and improve overall care.

5. Why is it so important to get teenagers into trials?

Trials make a real difference to patient survival. Regardless of whether the patient is on the best previous treatment or new experimental arm they appear to have improved survival. Trials make clinicians focus more carefully on therapy, supportive care and follow up and provide the 'best' evidence for the ''gold'' standards of care.

6. What special problems do teenagers with cancer encounter?

Firstly teenagers often ignore symptoms, putting them down to sport's injuries or being tired. The young person is in the process of developing independence so parents are less likely to nag them about going to the doctor. When they do finally seek medical help, GPs also do not always recognise young people get cancer, so there can be additional professional delays, especially if referral patterns are somewhat haphazard.

The emotional side should not be forgotten. Growing up is a traumatic period even without cancer. It's a time when people are becoming increasingly independent, but life-threatening conditions disrupt this aspect of development.

7. What special facilities do teenagers need?

The Teenage Cancer Trust has made big strides in the UK pioneering units for teenagers and young adults that provide health care in suitable environments. It is just not appropriate teenagers receive hospital treatment along side young children or older people – as we all know they keep totally different hours. If you try to impose rules of adult wards on teenagers it leads to rebellion. In our specialist teenage units we have adapted the rules and asked patients what they want. As a result we provide facilities like computer games and pool tables to promote feelings of ''normality''. Anxiety levels are reduced and recovery periods shortened.

8. What research are you involved in?

We are looking to see whether the biology of childhood tumours when they occur in this age range is the same or different? Is the cancer initiated in utero, as for children, or are different mechanisms involved? How important is genetic susceptibility? Our work involves a combined approach from epidemiologists and laboratory scientists looking at molecular pathways controlling DNA damage, recognition and repair.

For each tumour we are asking if there is a tumour specific trial available, and if not why not? We have to increase the rate of trial entry for this age group. We are also looking to optimise care by applying pharmacokinetics and pharmacodynamics principles to chemotherapy. Finally I am immensely keen to empower young people to take control of their lives and cancer. To this end we are exploring interventions to improve information giving, patient support and self-esteem.

9. What's happening to teenagers in other parts of the world?

We know that US, French, German and Dutch colleagues are all starting their own initiatives, but do not have that much of a handle about what is going on. I would be very interested to hear from health professionals in Europe and Worldwide about what they are planning for teenagers and young adults so that we can work together in moving the field forward.

Professor Tim Eden can be contacted at tim.eden@manchester.ac.uk