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Beyond Gleevec – the next generation in CML

Treatment options for chronic myeloid leukemia (CML) continue to expand, with second generation drugs going beyond imatinib (Gleevec®), delegates heard at the 47th Annual Meeting of the American Society of Hematology, December 10–13 (Atlanta, Georgia).

"Taken together the studies represent good news for CML patients doing less well on imatinib and point to a future where we'll use multiple drugs, as in HIV, to reduce leukemia load," said Dr. Hagop Kantarjian, from Anderson Cancer Center (Houston, Texas), adding the studies offer a paradigm for other cancers in development of targeted therapies based on mechanisms of resistance.

Since its introduction in 2001, imatinib, which inhibits the abnormal BCR-ABL fusion protein (derived from the Philadelphia chromosome, which drives the overproduction of abnormal white cells) has transformed treatment of CML. Studies show that when disease is reduced by greater than 3 logs, only 0.4% of patients suffer recurrence each year.

The latest results from the IRIS study (abstract 163), initiated in June 2000, comparing imatinib with interferon-alfa plus cytarabine, showed that at 44 months, 75% of patients demonstrated a reduction of at least 3 logs of BCR-ABL transcript levels. Of these patients, 51% had a 3-log reduction at 1 year, while 49% did not. "The results show ongoing disease elimination with time, and that patients in complete cytogenetic response who had adequate reductions in their BCR-ABL transcript levels at 1 year have a good chance of achieving a much greater reduction after 4 years of treatment," said principal investigator, Professor John Goldman from Imperial College (London, UK).

However, it has become recognised some patients face the challenge of developing resistance to imatinib, often due to acquired mutations in the BCR-ABL coding region affecting binding of imatinib to its ATP binding pocket. Insights into the mechanisms responsible for the acquisition of resistance resulted in development of two second-generation tyrosine inhibitors – dasatinib and AMN107. Both demonstrate pre clinical activity against 18 of 19 imatinib-resistant BCR-ABL mutants, with the exception of the T315I mutation. In addition, dasatinib also inhibits SRC protein kinases, which may provide real benefits since these enzymes play a role in the proliferation of CML cells.

Six month data from the START-C phase II study, undertaken in 75 institutions in 20 countries, show dasatinib to be effective in patients intolerant or resistant to imatinib with chronic phase CML, accelerated phase chronic CML and with chronic CML in blast crisis.

Dr. Andreas Hochhaus, from the University of Heidelberg (Mannheim, Germany) presented data for 186 patients with chronic phase CML resistant to imatinib (abstract 42). At 6 months 90% reached a complete hematologic response (defined as control of white blood cell counts) and 45% achieved a major cytogenetic response (defined as elimination of cells with the cancer-causing defect). Dr. Francois Guilhot, from The University Hospital (Poitiers, France) presented data in 99 patients with accelerated phase chronic CML, resistant to imatinib (abstract 39). Results showed 59% achieved a major hematologic response and 31% a major cytogenetic response.

Finally, Dr. Moshe Talpaz, from Andersen Cancer Center (Houston, Texas) presented data on 68 patients with chronic CML in blast crisis (abstract 40). He showed 31% reached a major hematologic response and 29% achieved a major cytogenetic response. The phase II data is being submitted for registration.

In the same session, Dr. Kantarjian presented results of a phase I study using AMN107 in 119 patients with imatinib-resistant CML in blast crisis or with philadelphia chromosome-positive acute lymphoid leukemia (abstract 37). Results showed that 60% achieved a hematologic response and 41% a cytogenetic response.

Dr. Hochhaus concluded: "We expect that when the results of these studies become mature the second generation tyrosine kinases will become the first choice of treatment."

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Combination therapy improves outcome in multiple myeloma

Combining lenalidomide (Revlimid®) with dexamethasone in previously treated multiple myeloma (MM) patients leads to significant improvements in the time to disease free progression compared to dexamethasone alone, concluded two parallel studies presented at ASH (abstract 6). The investigators predict this combination could become the new standard of care for MM.

In 2 separate phase III studies, overall involving 700 patients from North America, Europe, Israel and Australia, patients with relapsed or refractory MM were randomized to receive lenalidomide plus dexamethasone or dexamethasone plus placebo.

In 1999 thalidomide emerged as a new therapy for MM, but its use was limited by side effects including tetrogenicity, sedation, constipation, severe headache, tremor, deep vein thrombosis and peripheral neurophy. Lenalidomide is an analogue developed to overcome these effects. The idea to combine lenalidomide with dexamethasone came after a phase II study of lenalidomide showed the 30% of patients who did not respond did better when dexamethasone was added.

Results show the overall response rate was greater in patients who received lenalidomide plus dexamethasone than patients taking dexamethasone alone (58% versus 22%; $p < 0.001$); and that the median time to disease progression with lenalidomide plus dexamethasone was 49 weeks, compared with 20 weeks for placebo plus dexamethasone ($p < 0.001$). As of June 2005, median overall survival in patients treated with lenalidomide plus dexamethasone had not been reached as compared to 104 weeks with dexamethasome plus placebo ($p = 0.013$).

Professor Meletios Dimopoulos, from the University of Athens School of Medicine, Greece, who led the European part of the trial, commented: "These patients were running out of options. I believe that such combinations of treatments will contribute to the transformation of MM into a chronic disorder where people may live for 10–15 years or more."

In both trials the overall risk of thrombosis was 10%. The investigators believe that prophylactic anti thrombotic therapy should be considered for patients undergoing treatment with the combination. Lenalidomide is currently under review by the FDA.

Maintenance Rituximab in NHL produces survival benefits

Two year maintenance therapy with rituximab (MAThera) produces beneficial effects in overall survival in patients with non hodgkin's lymphoma (NHL)a, including those who have already received rituximab as part of their initial therapy, delegates heard at the ASH meeting (Abstract 353).

In the EORTC phase III study, patients with stage III or IV follicular lymphoma (FL) at initial diagnosis who had relapsed or proved resistance after a maximum of 2 non-anthracycline containing systemic chemotherapy regimens, were randomized to remission induction with either 6 cycles of CHOP (once every 3 weeks) or CHOP plus rituximab. Those with a complete or partial remission after 6 cycles of therapy underwent a second randomization to either no further treatment or maintenance therapy with rituximab once every 3 months, until relapse or a maximum of 2 years.

Results of the study on 369 patients show that those who received maintenance therapy has an overall survival of 85% at 3 years, compared to 77% for patients who received no maintenance therapy ($p < 0.011$). This translated to a risk reduction of 48%.

In addition, a highly significant advantage was seen for progression free survival for those randomized to the maintenance arm as opposed to the observation arm (median PFS 52 versus 15 months ($p < 0.0001$). This translated to a risk reduction of 60%.

Results of the induction phase of the trial showed that patients who received rituximab and CHOP had significantly higher rates of complete remission than patients who received CHOP alone (29% versus 16%, $p < 0.0001$).

Principal investigator Professor Marinus van Oers, from the Academic Medical Center of the University of Amsterdam, said: "We have not seen such an impressive improvement in progression free and overall survival for indolent NHL in the last 30 years. Maintenance therapy with rituximab may well become the standard of care for these patients."

Based on this data Roche filed with the EMEA (12 December) for a label extension to use rituximab as maintenance therapy in indolent lymphoma patients.

Darbepoetin helps chemotherapy induced anaemia

Administering darbepoetin to cancer patients undergoing chemotherapy is an effective strategy to control anaemia and simplifies treatment, reported a phase III study presented at ASH (abstract 3556).

It is estimated that approximately 67% of patients undergoing chemotherapy become anaemic due to chemotherapy reducing the bone marrow's ability to produce red blood cells. This is a side effect that frequently goes unrecognized, and is often under treated.

The multi center study randomized 391 patients diagnosed with anaemia (hemoglobin levels less than 11 g/dL) and a nonmyeloid malignancy, who had been scheduled to receive more than 12 weeks of chemotherapy, to receive darbopoetin (Aranesp®) or placebo.

Results showed that after 16 weeks 77% of patients achieved target haemoglobin levels in the darbepoetin group, versus 55% in the placebo group ($p < 0.001$). Additionally, from week 5 to the end of treatment, the incidence of red blood cell transfusions was significantly lower for the darbepoetin-treated group (24%) than for the placebo group (41%) ($p < 0.001$).

Lead investigator Dr. Kerry Taylor, from Mater Hospital, South Brisbane, Queensland, Australia, said: "If approved, this extended dosing of Aranesp® may allow physicians to treat anaemia on the same schedule as chemotherapy, which is frequently administered every 3 weeks. This may reduce the number of visits patients and their caregivers need to make to the clinic."

Replacing tamoxifen with aromatase inhibitor improves survival

Replacing tamoxifen with the aromatase inhibitor (AI) anastrozole significantly improves survival in early breast cancer patients compared to continuing on tamoxifen for 5 years, according to results from the first study to show survival benefits for changing hormonal therapy, presented at the 28th Annual San Antonio Breast Cancer Symposium (8–11 December 2005; San Antonio, Texas).

The meta-analysis of three trials with similar design – ABCSG Trial 8, ARNO 95 and the ITA trial – included a total of all 4006 women with hormone-sensitive early breast cancer who were randomized to switch to anastrozole after 2–3 years of tamoxifen or to remain on tamoxifen for 5 years. The population was considered representative of postmenopausal women with early breast cancer treated with adjuvant tamoxifen, although 99% of patients in the ITA trial were node-positive compared to about one-quarter in the other studies. The median follow-up was 30 months.

Results show women changing to anastrozole gained a 29% improvement in overall survival compared to those remaining on tamoxifen (hazard ratio 0.71; 95% CI 0.52–0.98; $p = 0.038$). The risk of disease recurrence was reduced by 45% (HR 0.55; CI 0.42–0.71; $p < 0.0001$ and risk of distant recurrence fell by 39% (HR 0.61; 95% CI 0.45–0.83; $p = 0.0015$).

Reporting the findings, Professor Walter Jonat, from University of Kiel, Germany, said: "The ultimate goal of the treatment of early breast cancer is to improve survival. Results from a previous study – the ATAC trial – showed survival is improved if patients start treatment with an AI rather than tamoxifen. This meta-analysis shows survival is also increased if patients already on tamoxifen are switched to anastrozole."

In a further trial of AIs, analysis of hazard ratios for disease recurrence over time between letrozole and placebo arms of the phase III MA17 study indicated patients gained greater benefits the longer they were treated, at least out to 4 years. Results for patients randomized to placebo showed increasing risk of disease recurrence over time after discontinuing prior tamoxifen, while the risk of recurrence for patients given letrozole peaked around 2 years of treatment before falling. The hazard ratio (letrozole/placebo) for recurrence showed a statistically significant ($p = 0.02$) trend to decrease over time, falling from 0.52 (95% CI 0.40–0.64) at 12 months to 0.19 (95% CI 0.04–0.34) at 48 months, indicating greater benefits with time.

Studies show gene signatures identify risk of breast cancer progression

Use of a 76-gene prognostic signature proved to have good sensitivity and specificity in identifying patients at high risk of distant metastasis in a multicentre study of patients with lymph node-negative (LNN) breast cancer. The study, presented at the San Antonio meeting, analyzing expression of 76 genes in frozen tissue samples from 180 patients, used a custom-designed Affymetrix VDX2 GeneChip. Results showed a hazard ratio for distant metastasis within 5 years of 7.41 (95% CI 2.63–20.9), even when corrected for traditional prognostic factors in multivariate analysis (11.36 [2.67–48.4]). The sensitivity for distant metastasis free survival was 90% and specificity 50%. Results were similar in a smaller group of women with oestrogen receptor positive tumours treated with tamoxifen.

John Foekens, Erasmus MC, Rotterdam, said: "Our data provide a strong methodological and clinical multicentre validation of the pre-defined prognostic 76-gene signature. It worked well in identifying patients with a good or bad prognosis."

A second study using a 21-gene recurrence score assay (Oncotype DX 21-gene test) showed it identified patients with early stage breast cancer at risk of loco-regional recurrence. It included a total of 1674 patients from 2 previous trials run by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-14 and B-20) – 895 of these had been treated with tamoxifen, 424 with chemotherapy plus tamoxifen and 355 with placebo. RNA from tumour samples was analyzed for expression of a set of 21 genes previously shown to predict breast cancer recurrence and survival.

Results showed a clear association between expression of the 21 genes (known as recurrence score) and the risk of local recurrence. Loco-regional recurrence in tamoxifen-treated patients was significantly associated with recurrence score – patients with a high risk score had a 15.8% 10-year event rate compared to only 4.3% in those with a low risk score ($p < 0.00001$). There were also similar associations in placebo-treated patients from B-14 ($p = 0.022$) and in tamoxifen plus chemotherapy-treated patients from B-20 ($p = 0.028$).

1% VTE risk at one year with breast cancer

Approximately 1 in every 100 patients with breast cancer develops venous thromboembolism (VTE) within 1 year of diagnosis, according to a large population-based study, presented in San Antonio.

The California Cancer Registry was merged with the California Patient Discharge Data Set, and the number of VTE events determined among 108,255 cases of breast cancer diagnosed between 1993–95 and 1997–1999 with at least 2 years follow up. Analysis revealed the cumulative incidence of VTE was 975 cases (0.9%) after 1 year, and 1306 cases (1.2%) after 2 years. The incidence rate was 0.9 events per 100 patient-years during the first year, falling slightly to 0.7 during year 2.

Metastatic disease was the strongest predictor of VTE (HR = 6.5, 95% CI 5.3–7.9 for metastatic versus localised disease). Surprisingly, women having breast cancer-related surgery within 61 days of diagnosis had significantly lower risks of VTE (HR = 0.6, 95% CI 0.5–0.7). For all cancer stages, diagnosis of VTE was associated with a higher risk of death within 1 year. Women with localized disease and a VTE were at 6 times the risk of dying within 1 year compared to those not suffering a VTE (HR = 6.0, 95% CI 3.4–10), while women with regional disease and a VTE had twice the risk (HR = 2.1, 95% CI 1.3–3.9) and those with metastatic disease had a 50% higher risk of dying (HR = 1.5, 95% CI 1.3–1.8).

EUROFILE

Getting EU populations health literate

"A key issue of European health policy is to enable and empower individuals to take increased responsibility for their health in their everyday lives," said Professor Ilona Kickbusch, Senior Advisor Health Policy, Bundesamt für Gesundheit, Bern, Switzerland, speaking at a forum on health literacy, held at the European Health Forum, Gastein, Austria, in October 2005.

Nearly every choice in modern life in Europe is connected in some aspects to health. The notion of health extends beyond the health system to all sectors of life and managing personal health is more than the knowledge and ability to adopt healthy lifestyles. Increasingly, health skills have become part of the life skills needed to navigate modern society, and are subject to rapid and continuous change. Health literacy was a critical strategy for the empowerment of citizens, communities, consumers and patients in Europe in order to enable them to make healthy choices in complex new health environments, Kickbusch said.

Speakers called for health literacy to be added to the three current literacies – basic, digital and information society literacy – emphasised by the European Commission's policy area on Lifelong Learning.

The Commission policy says that "Literacy is part and parcel of the pursuit of freedom, itself a central tenet of development". Health literacy, said speakers, was the ability to make sound health decision in the context of everyday life – at home, in the community, in the workplace, the health care system, the market place and the political arena. A high level of health literacy would enable citizens to navigate the rapidly changing health environment.

Enabling good health for all was key to European progress, said Kickbusch. "But even if the average European was healthy, good health for all is still not the rule. Organisation for Economic Co-operation and Development (OECD) statistics show that life expectancy for men in the EU varies from 64 to 77 years, the incidence of lung cancer varies by 5 times and suicide death rates vary from 4.9 (death rate by 100,000 males) in Greece to 44.4 (death rate by 100,000 males) in Hungary."

The Gastein forum looked particularly at the case of obesity, which has clear relevance to cancer as well as many other serious diseases. Peter Kopelman, from the European Society for the Study of Obesity, said that solutions to the obesity problem had to be long-term, and tailored to individuals. The media were responsible for the increasing information overload on health, and despite advances in health, it was often difficult to get the message across, he said. "Communication from health professionals is only slightly improved and they are failing to reach people of low socio-economic status, where obesity is most prevalent."

Insufficient and poor Health Literacy can lead to inefficiencies in society at large, but specifically in healthcare systems, speakers said. While empirical data on the effects of low Health Literacy in Europe were limited, research from the US Centre for Health Care Strategies concluded that individuals with low Health Literacy are less likely to understand written and oral information from health professionals; act upon necessary procedure and directions (such as medications and appointments); and be able to navigate the health system to obtain necessary services.

Peggy Maguire, Director General of the European Institute of Women's Health, pointed out the significance of demographic changes across Europe. Economic, social, political and cultural trends would influence how women lived their lives and also have important consequences for women's health and their quality of life. Women were increasingly heading up households in a way that was unthinkable in the latter half of the last century. Much of the responsibility for long-term care continued to fall on families, and it was largely women who continue to meet the majority of society's caring needs. The increasing prevalence of chronic illness and disabling conditions – together with the rising age of the population, were large contributors to the growing burden of disease.

"If people are to make healthy choices, we have to build a knowledge base on why different population groups make certain lifestyle choices, and we have to target health promotion and disease prevention information to specific groups by involving them in the development of information and education programmes. If people are to take responsibility for their health, they have to have access to the knowledge, skills and tools that enable them to make confident, healthy lifestyle choices. Giving them the ability when they are ill to navigate increasing complex health systems, enables them to understand medical advice. Health information and education must take a lifespan approach from children, to teenagers, to the elderly – it is part of the process of lifelong learning," she said.

Many speakers underlined the value the EU could add to the health literacy research agenda: by increasing the demand for health literacy; by creating, or supporting the creation of, a health literacy network; by putting the subject on the agenda of the EU Health Policy Forum; by supporting new joint programmes on public health and consumer policy; and by encouraging forthcoming presidencies to put health literacy on their agendas. The Finnish Presidency, which runs from July to December 2006, has already indicated that it will do so. It seems likely that we will be hearing much more about European health literacy in the years to come.

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PODIUM

Putting Europe in the driving seat

Professor Alexander Eggermont

Professor Alexander Eggermont, head of surgical oncology at the Erasmus University Medical Centre – Daniel den Hoed Cancer Centre, Rotterdam, was elected president of the European Organisation for Research and Treatment of Cancer (EORTC) in 2003. Here, he talks about the need for new translational research initiatives to place European oncologists at centre stage in clinical cancer research and drug development.

What's the history of the EORTC?

The EORTC was founded in 1962 to conduct, co ordinate, and stimulate research in Europe to improve the management of cancer. It was recognised this could best be accomplished through the multidisciplinary, multinational efforts of basic research scientists and clinicians. The EORTC facilitates the passage of experimental discoveries into state-of-the-art treatment and aims to minimise delays between the discovery of new anti-cancer drugs and their therapeutic benefit for patients. It's the only pan European clinical cancer research organisation.

How's the EORTC organised?

The EORTC infrastructure consists of 18 tumour groups and 3 laboratory science groups with networks of 1500–2000 investigators. Around 100 clinical trials are running at present, involving some 35,000 patients. Investigators work on a voluntary basis, with lots of dedication and enthusiasm driving the machinery.

The Data Centre at EORTC headquarters in Brussels, with around 100 staff, offers important support functions, such as data management, statistical design and analysis and regulatory affairs.

What trials do you organise?

A major component of the EORTC program consists of non-sponsored academic trials regarding surgical methods, radiotherapy regimes, and systemic therapy combinations to define new standards of care. Typically, it's impossible to get pharmaceutical sponsorship as the studies involve combinations of drugs that may have been registered for several years. Yet such studies are vital to define new standards of care and the EORTC is committed to perform them.

Apart from academic trials the EORTC is involved in fully sponsored drug development trials, including pivotal phase III trial for registration. For this we have developed flexible mechanisms where the monitoring and part of data listings are out sourced, but the hard-core scientific evaluation and quality assurance is undertaken by us. Everyone's a winner. The pharmaceutical industry gets trials that have been independently evaluated, while we receive money to finance academic trials.

How else is the EORTC funded?

Funding represents a major headache. We get part of our money from the EORTC foundation organizing charitable events and from cancer leagues across Europe making annual donations. We've, however, found it impossible to get any core funding from the EU. I find it totally ironic we receive a core grant from the National Cancer Institute (NCI); but not from Brussels. It reflects a lack of awareness of scientific issues among the European population and their politicians.

What effects has the clinical trial directive had on your work?

The directive has increased the costs of academic trials 2- to 3-fold. Moreover, it's made clinical trials more time consuming to organize and its hard to recruit clinicians who are aware of the extra time it eats up. At the institution level across Europe we're seeing a 50% reduction in the number of clinical trials taking place.

What message would you like to give to any oncologist thinking of participating?

The message is to come and join us and find out how educational and inspiring participation in tumour groups and their trials can be. Despite requiring an investment of time, it'll be an enjoyable part of your professional portfolio, generating real scientific interest. Taking part will also benefit patients, since it's well known people who participate in clinical trials do better and that they improve the overall organisation of care.

What would you rate as the EORTC's main successes?

The main success of EORTC is the creation of multinational, multidisciplinary trial networks, that have led to new standards of care being defined in many tumour types over the last 40 years.

The translational research projects have provided better understanding of the biology behind success and failure and define the next trials to be performed. We've a very good publication record and in the last 18 months have had 4 NEJM papers, 3 Lancet and some 10 Journal of Clinical Oncology papers. Not bad for a modestly funded voluntary organisation.

What challenges do you still face?

EORTC has always been particularly active in trials in rare tumour types since multi-national scenarios are the only option here. Increasingly, national networks have organized trials in common tumours such as lung, breast, colorectal and prostate cancer. But now that, for instance, breast cancer is dividing itself up iton perhaps as many as 10 different cancers, international collaboration is needed in all fields. The EORTC need to develop Intergroup Trial mechanisms to accommodate this need. Moreover, translational research is mandatory now and complicates these trials further especially in terms of logistics, regulatory issues and quality control. All this is very expensive and labour intensive, but we are ready to assume this role.

How are you encouraging participation?

To achieve this end we're setting up a network of core cancer institutes (NOCI) with high accrual as well as high performing laboratories, to undertake the analysis. We plan to hold the second meeting of the network in Brussels in March 2006 together with the chairs of all tumour and laboratory groups.

How can we improve things for Europe?

Europe – with its population of 500 million – has a tremendous opportunity to take the international lead in drug development. But the problem we face is that European society doesn't have either a belief or awareness of science. We need to create patient platforms, as they have in the US, to push for clinical trials and persuade politicians to give a greater weighting to funding.