NEWSROUND

Selected reports edited by Janet Fricker

Nilotinib and dasatinib superior to imatinib in first-line CML treatment

➜ New England Journal of Medicine

After one year of treatment, nilotinib and dasatinib were both found to be superior to imatinib when used as initial therapy for chronic myeloid leukemia (CML) with respect to all endpoints, according to two separate phase III studies.

Imatinib, an inhibitor of the BCR-ABL kinase, is the standard first-line therapy for patients with chronic-phase CML. Eight-year follow-up of the IRIS study revealed that responses to imatinib were durable and have an acceptable adverse-event profile, with an estimated rate of overall survival of 85%. But in addition to a relatively low potency, imatinib is susceptible to resistance through a large number of different mutations in the BCR-ABL target as a consequence of the way it binds to the BCR-ABL kinase domain. Two second-generation BCR-ABL kinase inhibitors have been developed that are more potent than imatinib, and have activity against most imatinib-resistant mutations in BCR-ABL. Dasatinib and nilotinib have been approved as second-line treatments for patients with CML if imatinib therapy fails. The current studies were undertaken to compare dasatinib and nilotinib with imatinib in the first-line setting.

In the Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION) Hagop Kantarjian and colleagues, from the MD Anderson Cancer Center in Houston (Texas), randomised 519 patients with newly diagnosed chronic-phase CML, from 108 study centres in 26 countries, to dasatinib (100 mg once daily; *n*=259) or imatinib (400 g once daily; *n*=260). The rate of major molecular response was 46% for dasatinib versus 28% for imatinib (*P*<0.0001); and progression to the accelerated or blastic phase of CML occurred in 1.9% of those receiving dasatinib versus 3.5% on imatinib. Safety profiles for the two treatments were found to be similar.

"In our trial, dasatinib, as compared with imatinib was associated with significantly higher and faster rates of complete cytogenetic response and major molecular response. Given the established association between complete cytogenetic responses within the first 12 months after the initiation of imatinib therapy and superior long term progression-free survival, longer follow-up may show that dasatinib therapy improves the long-term outcomes in patients with newly diagnosed chronic-phase CML," write the authors.

In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients (ENESTnd) study, Giuseppe Saglio and colleagues, from the University of Turin (Italy), randomised 846 patients with newly diagnosed Philadelphia chromosome-positive chronic-phase CML to receive nilotinib twice daily (300 mg *n*=282; 400 mg *n*=281) or imatinib 400 mg once daily (*n*=283).

Results at 12 months show that the major molecular response was 44% for 300 mg nilotinib, 43% for 400 mg nilotinib and 22% for imatinib (*P*<0.001 for both comparisons). The rates of complete cytogenetic response by 12 months were significantly higher for nilotinib (80% for the 300 mg dose and 78% for the 400 mg dose) than for imatinib (65%) (*P*<0.001 for both comparisons). Patients receiving either the 300 mg dose or the 400 mg dose of nilotinib twice daily had a significant improvement in the time to progression to the accelerated phase or blast crisis, as compared with those receiving imatinib (*P*=0.01 and *P*=0.004, respectively).

It is clear, write the authors, that nilotinib is more effective than imatinib. "Further follow-up will provide information on the durability of responses, the development of treatment resistance, and the side-effect profile of nilotinib in the front-line setting," they conclude, adding that studies will also be necessary to evaluate cross-resistance mechanisms, sequencing of treatment options and combinations of agents.

In an accompanying commentary Charles Sawyers, from Memorial Sloan-Kettering Cancer Center in New York, writes, "Some observers may argue that 1 year is too early in the comparison to claim victory in a disease with a much longer natural history, but early, sustained complete cytogenetic response is a validated surrogate marker for survival in CML on the basis of previous trials of interferon."

There are modest differences in side-effects, he adds, that might lead patients to switch from one drug to another. "There have been associations with pleural effusions with dasatinib, biochemical changes in liver function and QT prolongation with nilotinib, and edema and mus-

cle cramps with imatinib. Ironically, imatinib may survive the challenge on the basis of economic rather than scientific factors, since it could be available in generic form as early as 2014."

■ G Saglio, DW Kim, S Issaragrisil et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *NEJM* June 2010, 362:2251–2259

■ H Kantarjian, N Shah, A Hochhaus et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *ibid* pp 2260–2270

■ C Sawyers. Even better kinase inhibitors for chronic myeloid leukemia. *ibid* pp 2314–2315

Adding heat improves chemotherapy results in sarcoma

➔ Lancet Oncology

Treating high-risk sarcoma patients with regional hyperthermia alongside chemotherapy was associated with a 42% reduction in the risk of local progression or death compared with chemotherapy alone, reports a phase III German study.

The rationale for using regional hyperthermia is that heat kills cells by direct thermal toxicity, thereby increasing the efficacy of chemotherapy and inducing tumouricidal immune responses. In randomised trials combining regional hyperthermia with radiotherapy, locoregional control and disease-free survival has been improved in patients with melanoma, recurrent breast cancer and cervical cancer.

Between July 1997 and November 2006, Rolf Issels and colleagues, from the University Hospital in Munich, Germany, randomised 341 patients, from eight centres across Europe and one centre in the US, to receive neoadjuvant chemotherapy of etoposide, iphosphamide, and doxorubicin alone (n=172) or combined with regional hyperthermia (n=169). Patients had adult-type soft-tissue sarcoma of at least 5 cm diameter, grade 2 or 3, deep to the fascia but with no evidence of distant metastases. Regional hyperthermia was undertaken with a system (BSD-2000) using radiofrequency to reach a target tumour temperature of 42°C (107°F) for 60 minutes on days one and four of each chemotherapy cycle during induction and post-induction therapy.

Results show that at two years the primary endpoint of progression-free survival was achieved in 76% of the hyperthermia group versus 61% of the chemotherapy-alone group (P=0.003). Secondary endpoints were also significantly better for the hyperthermia group. Disease-free survival was nearly double that of chemotherapy alone (32 vs 18 months, P=0.011), and the treatment response rate was more than double (28.8% vs 12.7%, P=0.002).

However, the addition of hyperthermia significantly increased the risk of leukopenia, (reported in 77.6% of the hyperthermia group versus 63.5% of the chemotherapy-alone group, P=0.005), and thrombocytopenia (17.0% vs 13.8%, P=0.42). This, the authors suggest, may be related to the heating field involving part of the bone marrow, especially in patients with large abdominal or pelvic tumours. Other hyperthermia-related adverse events included pain, bolus pressure and skin burn, which were mild to moderate in 40.5%, 26.4%, and 17.8% of patients, and severe in 4.3%, 4.9% and 0.6%, respectively.

"This therapeutic strategy offers a new treatment option and can be integrated in the multimodal treatment approach for these patients," conclude the authors.

"Whether a similar benefit will be seen in lower risk patients, and whether the safety profile will be the same, and hence the trade off between benefit and harm worthwhile, remains to be established."

In an accompanying editorial, Robert Benjamin, from the MD Anderson Cancer Center, said that there were questions over whether the findings could be extrapolated for widespread use, or whether the technique should be limited to centres of excellence. Additionally, patients with atypical lipomatous tumours (ALT; also known as well-differentiated liposarcomas) had been excluded from the trial, he added, making it important to undertake such studies before "hyperthermia can take its place in standard sarcoma management. A more contemporary preoperative and postoperative chemotherapy regimen could be included for those with high-grade tumours."

■ RD Issels, LH Lindner, J Verweij et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* June 2010, 11:561–570

■ RS Benjamin. Regional hyperthermia: new standard for soft-tissue sarcomas? *ibid* pp 505

Shark cartilage delivers no benefit in lung cancer

➔ JNCI

The anti-cancer drug AE-941, a shark cartilage derivative, does not improve overall survival in patients with inoperable stage III non-small-cell lung cancer, a study sponsored by the US National Cancer Institute has found.

The absence of blood vessels in shark cartilage, in addition to preclinical studies analysing cartilage extracts, have supported the hypothesis that cartilage contains inhibitors of angiogenesis. In 1993 the US television news programme *60 Minutes* ran a story about use of shark cartilage as a cancer therapy, and by 1997 prominent complementary and alternative medicine practitioners were recommending its use to cancer patients. More recently, surveys have suggested that 6%–25% of cancer patients now use shark cartilage.

Charles Lu and colleagues, from the MD Anderson Cancer Center, write that the impetus for undertaking the current randomised double-blind trial on shark cartilage comes from, "The widespread use of poorly regulated complementary and alternative medicine products, such as shark cartilage-derived agents, among patients with advanced cancer, a population likely to be vulnerable to unsubstantiated marketing claims."

Between June 2000 and February 2006, the investigators enrolled 379 newly-diagnosed untreated stage 3 non-small-cell lung cancer patients at 53 sites in the US and Canada, who

received standard treatment of induction chemotherapy and chemoradiation, and were randomised to be treated with either AE-941 (*n*=188) or placebo (*n*=191), both in the form of a liquid. Patients drank four ounces of the extract twice daily.

Results at a median follow-up of 3.7 years show that no difference was seen in overall survival, progression-free survival, time to disease progression and tumour response rates between the groups receiving AE-941 and the groups receiving placebo. The median survival period was 14.4 months (95%CI 12.6–17.9 months) in patients who received AE-941 versus 15.6 months (95%CI 13.8–18.1 months) in patients who received placebo (*P*=0.73). Furthermore, no differences between the two groups were observed in common toxic effects of grade 3 or higher, attributable to chemoradiotherapy.

"The addition of AE-941 to chemoradiotherapy did not improve overall survival in patients with unresectable stage III NSCLC. This study does not support the use of shark cartilage-derived products as a therapy for lung cancer," conclude the authors. " We hope that this trial will provide physicians with relevant evidence-based information that can be conveyed to cancer patients who inquire about the activity of shark cartilage in their disease."

AE-941, the authors add, was manufactured and developed as an anticancer drug. "Therefore, these results represent the highest level of clinical data available for the role of a shark cartilage-derived agent as a cancer therapy," they write, adding that a further strength of the study is that subjects were recruited from both academic and community oncology centres, thereby enhancing the generalisability of the findings.

One limitation of the study, write the authors, was the lack of available pharmacokinetic and pharmacodynamic correlative studies, which limited their ability to investigate explanations for AE-941's lack of activity. "AE-941 is a standardized extract of a natural product, and currently, the active molecules in this extract remain poorly understood. Therefore there have been no human pharmacokinetic studies or validated pharmacodynamic or predictive biomarkers of activity."

In an accompanying editorial Jeffrey White, from the Division of Cancer Treatment and Diagnosis at the National Cancer Institute, said, "The results of the current trial provide valuable information to health-care practitioners and patients for discussions about the use of shark cartilage in cancer management."

He added that questions might arise about the generalisation of these findings to other, or all, shark cartilage products, and the study was missing important information about the process of standardisation, the variability in the product, best dose and compliance.

■ C Lu, JJ Lee, R Komaki, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial . *JNCI* 16 June 2010, 102:859–865

■ J White. The challenge of rational development of complex natural products as cancer therapeutics. *ibid* pp 834–835

Once-only flexible sigmoidoscopy reduces colorectal cancer incidence and mortality

➔ The Lancet

Offering single flexible sigmoidoscopy examinations to individuals aged between 55 and 64 reduced the incidence of colorectal cancer by 33% and mortality by 43%, UK investigators report.

Colorectal cancer is the third most frequently diagnosed cancer worldwide, accounting for more than 1 million cases and 600,000 deaths every year. Since survival is strongly related to stage at diagnosis (with survival rates of 90% for localised cases) this highlights the importance of screening. Many countries currently offer biennial screening with faecal occult blood tests, which are estimated to reduce mortality by around 25%. Since most colorectal cancers arise from adenomas, two-thirds of which are located in the rectum and sigmoid colon, Wendy Atkin and colleagues from Imperial College in London, UK, set out to evaluate the benefits of one-time flexible sigmoidoscopy screening on the incidence of colorectal cancer and its associated mortality.

In the study, which took place in 14 centres in the UK, 170,432 men and women, aged between 55 and 64 years, were randomised to either the intervention group, who received flexible sigmoidoscopy (*n*=57,237), or to a control group who received no intervention (*n*=113,195). In order to take part in the study, subjects needed to be registered with participating general practices and to have indicated on previous questionnaires that they would accept an invitation for screening. Participants underwent flexible sigmoidoscopy with polypectomy for small polyps and referral for colonoscopy if they had polyps measuring 1 cm or larger, three or more adenomas, tubulovillous or villous histology, severe dysplasia or malignant disease.

Results show after a median follow-up of 11.2 years, 2524 participants were diagnosed with colorectal cancer (1818 in control group versus 706 in the intervention group) and 20,543 died (13,768 in the control group versus 6775 in the intervention group).

In intention-to-treat analyses, colorectal cancer incidence in the intervention group was reduced by 23% (HR 0.77, 95%CI 0.70–0.84) and mortality by 31% (HR0.69, 95%CI 0.59–0.82). Those who attended their invited screening session (ie disregarding those who did not attend) had a 33% lower risk of a colorectal cancer diagnosis than those in the control group (HR 0.67, 95%CI 0.60–0.76), and a 43% lower risk of death from colorectal cancer (HR 0.57, 95%CI 0.45–0.72). Furthermore, the researchers estimated that 489 people would need to be screened to prevent one death due to colorectal cancer.

"The results from our trial show that flexible sigmoidoscopy is a safe and practical test and, when offered only once to people between ages 55 and 64 years, confers a substantial and long lasting protection from colorectal cancer," conclude the authors.

A limitation of the trial, they add, is that rather than inviting the whole population aged 55–64 years for screening, the trial used a two-stage recruitment procedure whereby eligible individuals were randomly assigned only if they

had indicated in a questionnaire that they would be likely to attend screening. "This meant that the compliance rate in the trial was higher than would be expected in a population-based programme, at least in its early years," they write.

In an accompanying commentary, David Ransohoff from the University of North Carolina at Chapel Hill wrote, "The good news is that this size of benefit is large for any cancer screening test, certainly compared with mammography for breast cancer or assay of prostate specific antigen for prostate cancer. On the other hand, a 50% reduction of colorectal cancer incidence (for lesions reached by the scope) is lower than figures popularly quoted for colonoscopy, but on the basis of non-randomised data. Perhaps even greater reduction for screening sigmoidoscopy will be observed after more follow-up."

He added that there remained questions of whether more frequent endoscopy might lead to still greater reductions in colorectal cancer.

■ WS Atkin, R Edwards, I Kralj-Hans et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 8 May 2010, 375:1624–1633

■ DF Ransohoff. Can endoscopy protect against colorectal cancer? A RCT. *ibid* pp1582–1584

Single-dose radiation found to be effective for early breast cancer

→ The Lancet

A single dose of radiation administered during surgery was found to be as effective as standard radiation therapy for women with early forms of breast cancer, reports the TARGIT-A study.

Breast-conserving surgery followed by post-operative whole-breast external beam radiotherapy has become the standard of care for many patients with early breast cancer. While radiotherapy is safe and effective and the risk of side-effects is low, many patients find the duration of daily treatments inconvenient. Observational studies and randomised clinical trials have shown that more than 90% of recurrent disease is within the index quadrant, with multifocal or multicentric cancers in other quadrants of breast appearing to remain dormant for many years. This led Jayant Vaidya and colleagues, from University College (London, UK), to the idea that irradiation of the immediate vicinity of the primary tumour might be adequate for achieving local control of cancer.

The TARGIT-A (Targeted Intra-operative radiation therapy) trial, launched in 2000, was designed to determine whether single-dose intraoperative radiation is equivalent to standard external beam radiotherapy using linear accelerators to irradiate the entire breast externally over three to six weeks. The TARGIT approach, pioneered by the UCL group, utilises a device that provides a point source of low energy X-rays positioned in the tumour bed for between 20 and 35 minutes to irradiate tissues at highest risk of local recurrence.

In the study, 2232 women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 28 centres in nine countries and assigned, in a 1:1 ratio, to receive targeted intraoperative radiotherapy (n=1113) or external beam radiotherapy (n=1119). Neither patients nor investigators were masked to the treatment assignment.

The primary outcome of the study was local cancer recurrence in the conserved breast. At four years there were six local recurrences in the intraoperative radiotherapy group (1.2%) versus five in the external beam radiotherapy group (P=0.41). Complication rates were similar for both groups: 3.3% in the TARGIT group and 3.9% in the external beam radiotherapy group, with the exception that wound seromas needing more than three aspirations were greater in the TARGIT group (2.1% vs 0.8%).

"This large, international randomised trial provides robust and mature evidence that substantiates previous findings showing that targeted intraoperative radiotherapy is safe. Rates of overall complications and major complications were similar in the targeted intraoperative radiotherapy and external beam radiotherapy groups," conclude the authors.

"Our results bring us closer to a scenario in which a patient with early breast cancer might complete all her local treatment, surgical excision, sentinel lymph node biopsy, and radiotherapy at one or two visits, without having to stay overnight in a hospital bed."

Biologically, write the authors, these results challenge two different dogmas. First that whole-breast radiotherapy is necessary in this group of patients and, second, that the traditional radiation dose (much higher than targeted intraoperative radiotherapy) is essential for effective tumour control. "Another interesting biological paradox is that the proportional risk reduction achieved by radiotherapy is the same whether the margins are positive, narrow, or wide," write the authors.

Advantages of intraoperative radiotherapy, they say, include avoiding irradiation of the intrathoracic structures (such as the heart, lungs and oesophagus), reductions in waiting lists for postoperative radiotherapy and cost savings. Longer follow-up is needed to monitor the clinical appearance of new primary tumours outside the index quadrant and delayed recurrences inside the index quadrant.

In an accompanying editorial David Azria and Céline Bourgier, from the Institut Gustave Roussy, in Villejuif, France, write that although the technique has been criticised since it was first developed, due to depth of dose, they are convinced that in elderly patients intraoperative radiotherapy offers "an excellent approach".

"It has been suggested that tamoxifen alone will be sufficient for patients aged 70 years or older. Local or regional recurrences at 5 years were significantly higher in the tamoxifen group than in the tamoxifen plus radiotherapy group. Accelerated partial-breast irradiation is therefore a better alternative than no irradiation at all, and should be widely proposed to these patients," they conclude.

■ J Vaidya, D Joseph, J Tobias et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 10 July 2010, 376:91–102

■ D Azria, C Bourgier. Partial breast irradiation: a new standard for selected patients. *ibid* pp 71–72