Dasatinib and nilotinib: effective alternatives to imatinib in CML and Ph-ALL?

Chronic myeloid leukemia (CML) is caused by upregulated activity of the ABL tyrosine kinase, which is encoded by the *BCR–ABL* fusion gene created by formation of the Philadelphia chromosome. Imatinib, an ABL tyrosine kinase inhibitor, is the first-line treatment for newly diagnosed CML, but mutations in the *BCR–ABL* gene can impair the ability of this drug to bind, causing drug resistance. Results from two phase I dose-escalation studies have been published that describe the efficacy of two BCR–ABL tyrosine kinase inhibitors, dasatinib and nilotinib, in imatinib-resistant patients with CML or Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph-ALL).

Talpaz *et al.* studied the effects of 15–240 mg/day dasatinib in 84 patients with CML or Ph-ALL who were resistant to or intolerant of imatinib. The drug led to complete hematologic responses in 37/40 patients with chronic-phase CML, and major hematologic responses in 31/44 patients with CML with blast crisis, accelerated-phase CML, or Ph-ALL. Dasatinib produced responses in all *BCR–ABL* genotypes apart from the T315I mutation, which had already been shown to be resistant to imatinib *in vitro*. Myelosuppression was common but not dose-limiting, and resolved in most patients who experienced cytogenetic remission; the authors nonetheless recommend further investigation of this phenomenon. Dasatinib did not lead to a recurrence of non-hematologic toxic effects in those patients who could not tolerate imatinib. Many patients with blast-crisis CML and Ph-ALL developed resistance to dasatinib, however, and the authors acknowledge that this might be the eventual outcome in many patients, although responses were maintained in 95% of the patients with chronic-phase disease, and 82% of those with accelerated-phase disease over median follow-up of 12 months and 5 months, respectively. These preliminary results nevertheless support the use of dasatinib as a single-agent therapy for imatinib-resistant CML and Ph-ALL. The drug recently received approval by the FDA for use in these conditions.

Kantarjian *et al.* treated 119 patients with imatinib-resistant CML or Ph-ALL with 50–1,200 mg/day nilotinib. The drug produced hematologic response rates of 74% and 39%, and cytogenetic response rates of 55% and 27%, in patients with the accelerated and blastic phases of the disease, respectively. Of the 12 patients with chronic-phase disease, 11 (92%) had a complete hematologic response. Nilotinib was not as effective, however, in patients with Ph-ALL. Like dasatinib, this drug was effective in cases with *BCR–ABL* mutations, but not in those with a T315I mutation. The toxic effects commonly seen with imatinib were not evident; however, some other adverse effects were seen, including myelosuppression, which was dose-related and dose-limiting. The authors conclude that nilotinib is active in CML and has a reasonably favorable safety profile, especially at an optimum dose of 400 mg twice daily. Nilotinib is still under review by the FDA.

The possibility that some *BCR–ABL* mutations may be targeted by imatinib but resistant to other kinase inhibitors suggests that combination therapy might be the best option for initial treatment of CML; successful long-term treatment might require a combination of several different kinase inhibitors. Phase II studies of several BCR–ABL inhibitors are ongoing.

Original articles Talpaz M *et al.* (2006) Dasatinib in imatinib-resistant Philadelphia chromosome–positive leukemias. *N Engl J Med* **354:** 2531–2541
Kantarjian H *et al.* (2006) Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. *N Engl J Med* **354:** 2542–2551

Oophorectomy reduces risk of ovarian cancer in *BRCA* mutation carriers by 80%

Oophorectomy is often advised for women with *BRCA1* or *BRCA2* mutations, who are at increased risk of ovarian, fallopian tube or peritoneal cancer. The reduction in cancer risk associated with the procedure is estimated to be 60–95%, but these estimates are based mostly on retrospective and cross-sectional studies. An international prospective study of *BRCA1* and *BRCA2* mutation carriers has estimated the risk reduction for ovarian cancer after oophorectomy to be 80%.

Finch *et al.* studied 1,828 women aged 30–75 years with *BRCA1* or *BRCA2* mutations, identified from an international registry. Of these, 555 women had prophylactic bilateral salpingo-oophorectomy before study entry, and