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News & Views

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1. Second generation TKIs come of age in CML

The updated results of the START programme demonstrate continued efficacy for dasatinib (Sprycel™) in Chronic Myeloid Leukemia (CML), and reported two studies presented at ASH.

In the phase II start C trial (abstract 734), 387 chronic phase CML patients with documented resistance to imatinib (Gleevec™) were switched to 70 mg dasatinib BID. At a median follow-up of 24 months, results showed that a major cytogenetic response occurred in 62% of patients, a complete hematologic response in 53% and a major molecular response in 47% of patients. Progression-free survival was 80% at 2 years (in comparison to 91% at 1 year), and the overall survival was 94% at 2 years (in comparison to 97% at 1 year).

“This represents an extraordinary achievement in CML patients who initially had a poor prognosis after failing imatinib,” said principal investigator Richard Stone (Dana Farber Cancer Institute, Boston, MA).

The results, he added, proved remarkably stable: of those patients who achieved a major cytogenetic response at 1 year, 88% held that response at 2 years. Furthermore, a mutation analysis revealed that only T315I mutation did not respond to treatment.

In the START R study (abstract 736), Hagop Kantarjian (MD Andersen Cancer Centre, Houston, Texas) showed that switching to dasatinib produced better patient outcomes than raising the imatinib dose in patients with imatinib resistance.

The phase II study randomized 150 patients with chronic phase CML resistant to imatinib 400–600 mg/d in a 2:1 basis

to dasatinib 70 mg BID ($n = 101$) or imatinib 800 mg/d ($n = 49$). The updated 2-year results show that progression-free survival was 86% for dasatinib versus 65% for imatinib ($P = 0.0012$), the complete cytogenetic response was 44% for dasatinib versus 18% for imatinib ($P = 0.0025$) and the major molecular response was 29% dasatinib versus 12% imatinib ($P = 0.028$).

“Together the START studies are changing the treatment paradigm,” said Kantarjian. “People who have failed imatinib should not now be considered for transplantation unless they’ve also failed a second generation TKI.”

2. Dexamethasone dose needs re-evaluation in multiple myeloma

Survival advantages are associated with lower doses of dexamethasone in patients with newly diagnosed multiple myeloma, concludes a study from the Eastern Cooperative Oncology Group (abstract 74).

The phase III study included 445 newly diagnosed patients randomized to receive either high- or low-dose dexamethasone in combination with oral lenalidomide (Revlimid). Overall survival at 1 year was 96% with low dose compared to 88% with high dose ($P = 0.003$). Overall survival at 2 years was 87% with low dose compared to 75% with high dose ($P = 0.009$).

“The study shows that use of high-dose dexamethasone needs to be completely re-evaluated in multiple myeloma,” said principal investigator S. Vincent Rajkumar (Mayo Clinic, Rochester, Minnesota, USA).

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ASH 2008 Meeting. Courtesy American Society of Hematology.

Richard Stone. Courtesy American Society of Hematology.

Reviewing 20 extra deaths in the high-dose steroid group, investigators found that only 10 could be attributed to toxicity, the remainder occurred as a result of progressive disease. Professor Brian Durie (Cedars Sinai Medical Center, Los Angeles, California, USA), one of the investigators, said that lowering the dose of dexamethasone is a new approach to treatment: "When we combine lenalidomide with lower dose dexamethasone we are seeing reduced side-effects with the result that patients stay on the drug longer, producing significant survival benefits," he said.

3. Radioimmunotherapy improves outcome for follicular lymphoma

A single infusion of a radioimmunotherapy agent given to patients with advanced follicular lymphoma significantly improved progression-free survival, reports a phase III study presented at ASH (abstract 643).

The Zevalin First-line Indolent Trial (FIT) study investigated the effect of a single dose of ^{90}Y -ibritumomab tiuxetan (Zevalin) (a combination of an anti-CD20 monoclonal antibody and a radioisotope) in patients with advanced (stage III or IV) follicular lymphoma who had achieved partial or complete remission after receiving standard chemotherapy.

Patients were randomized to receive consolidation with a single dose of ^{90}Y -ibritumomab tiuxetan ($n = 208$) or no further treatment ($n = 206$).

After a median observation period of 3.5 years, patients randomized to consolidation with radioimmunotherapy had a median progression-free survival of 37 months compared with 13.5 months for the control group ($P < 0.001$).

Separate analysis of treatment effect by initial response showed that patients who achieved a partial response to induction therapy had a median progression-free survival of 29.7 months with consolidation therapy compared with 6.3 months for the control group ($P < 0.0001$). Among patients who had a complete response, median progression-free survival was 54.6 months with radioimmunotherapy versus 29.9 months for the control group ($P = 0.01$).

FIT lead investigator Anton Hagenbeek (Academic Medical Centre, Amsterdam, The Netherlands) said: “I am particularly impressed that with one single infusion of Zevalin, we have achieved prolongation of Progression-Free Survival by two years, with a favourable toxicity profile. We hope that we will go on to see a difference in overall survival.”

Christian H. Geisler, MD, PhD, Pierre Fenaux, MD, Jane Winter, MD, S. Vincent Rajkumar, MD, Volker Diehl, MD, and Anton Hagenbeek, MD, PhD. Courtesy American Society of Hematology.

4. Intensified BEACOPP for Hodgkin's lymphoma

Intensifying a standard chemotherapy regimen improves overall survival in poor prognosis Hodgkin's lymphoma patients, concluded the German Hodgkin Study Group (abstract 211).

In the phase III trial Volker Diehl (University of Cologne, Cologne, Germany) randomized 1282 advanced-stage Hodgkin's lymphoma patients to receive one of three chemotherapy regimens.

The first was standard of care COPP (cyclophosphamide, vincristine, procarbazine and prednisone) alternating

with ABVD (doxorubicin, bleomycin, vinblastin, and dacarbazine), the second, standard of care BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) and the third escalated dose BEACOPP.

Results showed that escalated BEACOPP led to significant improvements in the 10-year overall survival rate standard BEACOPP (86% versus 80%, $P = 0.0053$) and over COPP-ABVD (86% versus 75%, $P < 0.001$).

Additionally, escalated BEACOPP increased 10-year freedom from treatment failure, with a rate of 82% for the escalated dose versus 70% for standard BEACOPP ($P < 0.0001$) and 64% for COPP-ABVD ($P < 0.001$).

The results, concluded Diehl, support use of escalated BEACOPP as first-line therapy in advanced-stage Hodgkin's lymphoma. There are, however, concerns around second malignancies such as myelodysplastic syndrome, with the 10-year data showing rates of 3.1%, 3.6%, and 3.2% for COPP-ABVD, standard BEACOPP, and escalated BEACOPP, respectively. In two other European trials, where escalated BEACOPP has since been used in more than 2500 patients, the leukemia rate dropped down to 0.9%.

He added that escalated BEACOPP has since been used in more than 2500 patients in two other European trials. “The leukemia rate dropped down to 0.9%,” he said. Patients had leukemia and Hodgkin's lymphoma simultaneously, he said, indicating that the treatment was not responsible.

Volker Diehl. Courtesy American Society of Hematology.

5. New era for mantle cell lymphoma

Intensive immunotherapy offers the potential to cure mantle cell lymphoma, concluded a late breaking abstract at ASH from the Nordic Lymphoma Group (abstract LB1).

Mantle cell lymphoma, a condition accounting for 6–10% of lymphomas, has been regarded as incurable, with a mortality of approximately 50% after 3–4 years, even with CHOP.

In an attempt to increase survival The Nordic Lymphoma Group investigators, led by Christian Geisler (Rigshospitalet, Copenhagen, Denmark), initiated an intensive regimen in 159 newly diagnosed primary stage IV MCL patients. Patients received six cycles of intensive induction immunochemotherapy

consisting of maximized CHOP chemotherapy and high-dose cytarabine plus concurrent rituximab. Responders then received high-dose chemotherapy (BEAM/BEAC) plus stem cell support.

The 5-year event free and overall survival rates from the MCL2 study were 63% and 75%, respectively, which were significantly higher than the MCL1 study 15% ($P < 0.0001$) and 41% ($P < 0.001$), respectively. The MCL1 regimen had not included rituximab. Of the 144 responders who completed treatment, 72% were without disease at 5 years.

There was also a strong molecular response with PCR measurement of the t(11;14)(q13;q32) translocation (the characteristic genetic abnormality of MCL) showing that 90% of analyzed patients given the MCL2 protocol achieved molecular remission and became PCR-negative versus 38% with the MCL1 protocol ($P = 0.0002$).

The addition of rituximab may have been responsible for the improved results, Dr. Geisler commented: “After 3 years, there emerged a plateau on the survival curve indicating for the first time that this disease may be cured,” he said. “Compared to the known historical data for this disease, we believe that we are at least allowed to say a cure is in sight. We believe that this is the beginning of a new era for the treatment of mantle cell lymphoma.”

6. Azacitidine becomes standard of care in high-risk MDS

For patients with high-risk myelodysplastic syndrome (MDS) azacitidine should be considered first-line treatment, reports a study at ASH (abstract 817).

Patients with high-risk MDS have a median survival of about a year, with most eventually developing bone marrow failure. The disease has no cure aside from bone marrow transplantation, which is appropriate for only a minority of patients.

In a phase III trial Pierre Fenaux (Hôpital Avicenne, Paris, France) compared azacitidine (Vidaza) with conventional care in 358 patients with high-risk MDS (defined by FAB subtype and an International Prognostic Scoring System score of INT-2 or higher). Conventional care included chemotherapy in 40% of cases, with the remaining patients received low-dose cytarabine or being treated with transfusions, antibiotics, and granulocyte-colony stimulating factor (G-CSF) for neutropenic infections.

Results showed that at a median follow-up of 21 months patients on azacitidine had a median overall survival of 24.4 months, compared with 15 months with conventional care (hazard ratio, 0.58; $P = 0.0001$). In addition, the 2-year survival rate was 50.8% with azacitidine, compared with 26.2% with conventional care (hazard ratio, 0.58; $P = 0.0001$).

“Our conclusion is that azacitidine should now be considered standard treatment for high-risk MDS,” said Fenaux, he added.

Azacitidine is an epigenetic agent that is thought to exert anticancer activity by means of DNA hypomethylation and a direct cytotoxic effect on abnormal hematopoietic cells.

Dr. Claude Nicaise.

7. Dr. Claude Nicaise, vice president of clinical development at Bristol-Myers Squibb, reviews recent advances in Chronic Myeloid Leukemia (CML) and looks to the future of treatment

7.1. How has the treatment of CML changed over the last 10 years?

Over the last 10 years CML treatment has gone from symptomatic treatment with cytotoxic agents, such as hydroxyurea, to the introduction of imatinib (Glivec®) in 2000 which was the first drug to inhibit Bcr-Abl, the abnormal protein responsible for the excess of white blood cells. The IRIS study, first published in 2003, represents a landmark in the treatment of CML since it was the first time investigators demonstrated that a large proportion of patients were in remission from the disease by eradication of the Philadelphia chromosome. The 5-year IRIS data, published in 2006, show that approximately 69% of patients who started treatment remain on imatinib after 5 years, and are in complete cytogenetic response, meaning that there is a complete absence of leukemic cells in the bone marrow by conventional or FISH cytogenetic testing. There are even patients in molecular response, where Bcr-Abl cannot be detected by PCR.

7.2. What happens to people who fail imatinib?

There are several ways people can fail imatinib. First, is progression where people stop responding to imatinib after developing resistance. People can develop specific mutations in Bcr-Abl, over-express Bcr-Abl or develop efflux mechanisms that pump drug out of the cell. Some patients can be rescued by escalating the dose of imatinib, but in most cases their response is not durable. Secondly, people are sometimes no longer able to receive imatinib because they become intolerant to the side-effects. To put into context, out of 10 patients started on imatinib, three will have been forced to discontinue

treatment by 5 years, pointing to the need for alternative tyrosine kinase inhibitors (TKIs).

7.3. What are the advantages of the new tyrosine kinase inhibitors?

The first cases of resistance to imatinib were discovered in 2001/2002. BMS's TKI dasatinib (Sprycel®) has been shown to retain its activity against all but one of the Bcr-Abl mutants, T315I. Dasatinib is also 300 times more potent than imatinib. One explanation for the increased potency appears to be that dasatinib binds to the open and closed conformation of Bcr-Abl, while imatinib only binds to the closed conformation.

7.4. How is dasatinib currently used?

Dasatinib received its EU licence in November 2006 and is currently approved for use second line in patients whose disease is unresponsive or resistant to imatinib. Used front-line dasatinib might offer the potential to promote a more profound response than imatinib. One study presented at ASCO last year demonstrated that dasatinib used front-line induced a complete cytogenetic response of 95% at 1 year, which appears to be a higher response than that reported for imatinib. Essentially if dasatinib proves more effective upfront it might result in the emergence of less resistance.

7.5. Why do people taking dasatinib appear to be more prone to the side-effect of pleural effusions than those taking imatinib?

All the TKIs cause fluid retention which appears to be associated with inhibition of the PDGF receptor. Imatinib and nilotinib cause peripheral odema, while dasatinib causes pleural effusions in 10% of cases. For the majority of people stopping treatment for a few days, and then starting again on a lower dose is sufficient to sort out the problem. In one recent study

we showed that the 100 mg once a day dose compared with 70 mg BID cut the rate of pleural effusions by half. The 100 mg dose has since become the standard treatment.

7.6. How has ASH 2007 taken the dasatinib story forward?

For me ASH 2007 represents a turning point in CML treatment. The START C and R study provides critical data showing that dasatinib produces a durable response that can be maintained over 2 years, providing long-term benefits to patients. The 2-year data in imatinib intolerant patients showed a major molecular response of 92% among patients in complete cytogenetic response which compares favourably with the recent IRIS study update. The data are even more striking when you bear in mind that this group of patients had a particularly poor prognosis because they had already received imatinib. We are now moving away from using dasatinib only in imatinib failure to using imatinib front-line in the early treatment of disease.

7.7. What does the future hold for CML?

Eventually we hope to offer personalised medicine for CML patients where we would select the TKI that offers the best balance of efficacy and tolerance for that individual. It's likely that combinations of the different TKIs could help people with resistance, and new drugs are in development with different mechanisms of action.

One of the critical questions we are trying to address is how to move to a complete cure where patients develop normal haematopoiesis and can stop taking drugs altogether. One of the important long-term questions we are addressing is whether the existence of dasatinib, a more potent inhibitor, might ultimately contribute to a long-term cure.

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