



## LANDMARKS

# EVIDENCE WATCH

## A review and assessment of recent clinical trial data

*Oncology Exchange* provides overviews of important clinical trial data presented at the 50<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH), held December 6–9, 2008 in San Francisco, California. Leading Canadian experts offer commentary and clinical interpretations.

Contributors were selected by Douglas Stewart, MD, FRCPC.

## Tyrosine kinase inhibitors in early chronic-phase CML

**A. Robert Turner MD, FRCPC**, Professor of Medicine, University of Alberta, and Cross Cancer Institute, Edmonton, AB

Cortes J, Baccarani M, Guilhot F et al. **A Phase III, randomized, open-label study of 400 mg versus 800 mg of imatinib mesylate (IM) in patients (pts) with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase (CML-CP) using molecular endpoints: 1-year results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) Study.** ASH 2008, Abstract 335.

**TRIAL SUMMARY:** The open-label, Phase III Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study randomized 476 newly diagnosed patients with untreated chronic-phase chronic myelogenous leukemia (CML) in a 2:1 fashion to receive imatinib 800 mg (n = 319) or 400 mg (n = 157) per day. The trial aimed to examine whether the 800-mg daily dose of imatinib would provide shorter times to major molecular response (MMR) and better long-term outcomes than the standard 400-mg dose. Enrollees' median age was 47 years, and 24% were Sokal high risk. Time to MMR was faster in the patients receiving the 800-mg/day dose compared to those receiving 400 mg/day (p = 0.0038). At 12 months, 62% of the 800-mg/day group and 85% of the 400-mg/day group were receiving their assigned dose; median dose intensity was 750 mg/day in the 800-mg arm and 400 mg/day in the 400-mg arm. As shown in **Table 1**, significantly more of the 800-mg/day patients achieved MMR at 3 months and 6 months, but not at 12 months (MMR rate at 12 months was the primary endpoint). The patients receiving 800 mg/day achieved faster complete cytogenetic response (CCR) rate, with a rate of 57% compared to 45% in the 400 mg group (p = 0.0146). At 12 months, while rates of MMR and CCR were higher in the 800 mg group, the differences were not statistically significant. The most common Grade 3–4 non-hematologic toxicities were rash,

**TABLE 1. Major molecular response rates at 3, 6 and 12 months in the intention-to-treat population in the TOPS study**

time	imatinib 800 mg/day (n = 319)	imatinib 400 mg/day (n = 157)	p-value
3 months	12%	3%	p = 0.0011
6 months	34%	17%	p = 0.0002
12 months	46%	40%	p = 0.2035

diarrhea and myalgia, occurring slightly more frequently in the 800-mg/day arm. Exploratory analysis of molecular response found that based on the BCR-ABL/control gene ratio at 6 months, 12-month MMR rates were 46% in the > 0.1% to ≤ 1% range, 14% in the > 1% to ≤ 10% range, and 18% in > 10% in the 800-mg/day group compared to 52%, 11%, and 0%, respectively, in the 400-mg/day group. They also found that plasma imatinib concentrations in the lowest quartile (< 1165 ng/mL) had slower time to MMR (p = 0.0149). Six patients (3 in each arm) progressed to aggressive and/or blast phase disease. The authors concluded that MMR occurred earlier in the patients treated with 800 mg/day, and that further followup will allow evaluation of the effect of dose and molecular response on long-term clinical outcomes.

Cortes J, O'Brien S, Borthakur G et al. **Efficacy of dasatinib in patients (pts) with previously untreated chronic myelogenous leukemia (CML) in early chronic phase (CML-CP).** ASH 208, Abstract 182.

**TRIAL SUMMARY:** This Phase II trial randomized 50 patients with previously untreated chronic-phase CML to receive the TKI inhibitor dasatinib 50 mg twice per day (n = 25) or 100 mg once per day (n = 25). Patients' median age was 45 years (range 18–76 years); 75% had Sokal low risk scores. As shown in **Table 2**, at median followup of 24 months, 44 (98%) of 45 evaluable patients had achieved CCR, comparing favourably to rates seen with imatinib 400 mg or 800 mg/day in historical controls. At 12 months, 12/35 (34%) patients achieved MMR, as did 12/25 (48%) at 18 months; complete molecular response was achieved by 1/46 (2%), with one other unconfirmed complete molecular response. Reported Grade 3–4 non-hematologic toxicities included pruritus (13%), fatigue (6%), neuropathy (4%) and memory impairment (4%); 21% of evaluable patients had pleural effusions (2% were Grade 3–4). Transient Grade 3–4 hematologic toxicities included thrombocytopenia in 11%, neutropenia in 21% and anemia in 9%, with 27 patients (54%) requiring transient treatment interruption. No significant differences were seen in Grade 3–4 toxicities between the two dosage

**TABLE 2. Complete cytogenetic response rate (CCR) in patients receiving dasatinib compared to historical controls at 24 months median followup**

time on therapy	Percent with CCR (number of evaluable patients)			p-value
	dasatinib	imatinib 800 mg	imatinib 400 mg	
3 months	78% (45)	62% (202)	37% (49)	p = 0.0003
6 months	93% (41)	82% (199)	54% (48)	p < 0.0001
12 months	97% (35)	86% (197)	65% (48)	p = 0.0001
18 months	88% (33)	89% (179)	68% (38)	p = 0.004
24 months	80% (25)	99% (173)	70% (40)	p = 0.006

schedules. Event-free survival at 24 months was 81%, with events defined as loss of complete hematologic response, loss of major cytogenetic response, accelerated phase and/or blast phase, death or toxicity-related study withdrawal. The authors concluded that dasatinib treatment achieved rapid CCR in most patients with previously untreated chronic-phase CML, with a favourable toxicity profile.

Rosti G, Castagnetti F, Poerio A et al. **High and early rates of cytogenetic and molecular response with nilotinib 800 mg daily as first line treatment of Ph-Positive chronic myeloid leukemia in chronic phase: results of a phase 2 Trial of the GIMEMA CML Working Party.** ASH 2008, Abstract 181.

**TRIAL SUMMARY:** This interim report of a Phase II open-label study by The Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) CML Working Party examined results of treatment using the second-generation tyrosine kinase inhibitor (TKI) nilotinib (400 mg twice per day) in 73 patients with untreated, early chronic-phase, Philadelphia-positive (Ph+) CML. Participants had a median age of 51 years (range 18–83); 45% had low Sokal risk scores; 41% were intermediate-risk and 14% were high-risk. Due to dose reductions and omissions because of adverse events, the median daily average dose was 789 mg (range 261–800 mg). At median followup of 210 days (range 68–362 days), with all 73 patients completing 3 months of treatment and 66% completing 6 months, the complete hematologic response rates were 100% at 3 months and 98% at 6 months; the CCR rates were 78% and 96%, respectively (the primary endpoint for the study is CCR

rates at 12 months). At 6 months, 74% of patients had a MMR, defined as a BCR-ABL:ABL ratio < 0.1% according to the International Scale. Rates of MMR were of 3% after 1 month, 22% after 2 months and 59% after 3 months. Four patients (5%) experienced hematologic toxicities, including one case of Grade IV neutropenia; 15% of patients had increased bilirubin, 11% had increased glutamic-oxaloacetic transaminase and/or glutamic-pyruvic transaminase (GOT/GPT) and 4% had increased lipase. Incidence of Grade 2 non-hematologic events declined between the first and second 3-month period. Sixteen patients (22%) had transient, non-clinically relevant electrocardiogram abnormalities, and two more (3%) had transient QTc prolongation in their electrocardiograms. The authors concluded that treatment with nilotinib in this population appears to provide faster cytogenetic and molecular responses than imatinib, with a manageable toxicity profile.

**COMMENTARY:** In the December 7, 2006 issue of the *New England Journal of Medicine*, Brian Druker and colleagues reported on the 5-year followup of the IRIS study,<sup>1</sup> in which patients with Ph+ CML were treated with 400 mg imatinib mesylate daily.<sup>2</sup> The overall survival was 89% at

60 months, and only 7% of patients had progressed to the accelerated or blast-crisis phase. Among the patients with CCR at 12 months, 97% did not progress to an advanced disease phase, irrespective of Sokal score. Of those patients whose CCR was associated with > 3-log reduction of levels

of BCR-ABL transcripts, none progressed. These results have set a very high bar for acceptance of an alternative approach to newly diagnosed patients. Imatinib at a dose of 400 mg daily provides a complete cytogenetic response in 87% of patients, and > 3-log reduction of BCR-ABL transcripts in 36%. Rates of intolerance are very low and results appear to improve over time.

At the American Society of Hematology 2008 Annual Meeting, my colleagues and I reported an 83% 5-year survival rate for patients in a population registry-based analysis of the impact of BCR-ABL-specific TKI inhibition on survival after diagnosis of Ph+ CML in patients treated from 2000 to 2006.<sup>3</sup> This “real world” outcome is impressive and makes one reluctant to change practice. The three papers summarized above presented preliminary results for three alternative therapies for newly diagnosed CML patients. One reported on increasing the dose of imatinib to 800 mg daily (TOPS). Another used dasatinib 50 mg twice daily or 100 mg daily.

**TABLE 3. Complete cytogenetic response (CCR) and molecular response (MR) at one year in studies of different agents used to treat chronic myelogenous leukemia**

	imatinib (IRIS <sup>2</sup> )	imatinib (TOPS)		dasatinib	nilotinib
	400 mg/day	400 mg/day	800 mg/day	100 mg/day	800 mg/day
<b>number of patients</b>	553	157	319	50	73
<b>median age (years)</b>	50	47	47	45	51
<b>Sokal score*</b>					
<b>low</b>	52%	-	-	75%	45%
<b>intermediate</b>	29%	-	-	-	41%
<b>high</b>	18%	24%	24%	-	14%
<b>CCR</b>	69%	45%	57%	97%	96% (at 6 months)
<b>&gt; 3-log MR</b>	37%	40%	46%	34%	74% (at 6 months)

\* achieving CCR by 12 months obliterates the negative prognostic effects of Sokal score

The third, also the smallest and shortest, study looked at nilotinib 400 mg twice daily. As shown in **Table 3**, each of these studies reported very high rates of complete hematologic remission, early CCR and > 3-log reduction of BCR-ABL, with low toxicity rates.

The TOPS study was the largest and was randomized. The results reported from the 400 mg imatinib cohort are similar to the IRIS results except for a much lower CCR rate at 12 months. The authors conclude that MMR occurred earlier in the patients treated with 800 mg per day but that there was no significant difference in CCR rates or MMR rates at 12 months.

Both the dasatinib and nilotinib trials were small. The dasatinib study had a much larger proportion of patients with low Sokal scores. The nilotinib study reported a very high rate of major molecular response at 6 months (approximately twice that reported in the other studies). Both the dasatinib and nilotinib trials reported an exceedingly high CCR rate at 12 and 6 months, respectively.

The very high rates of CCR

## In brief

### Already known

- Studies of patients with chronic-phase chronic myelogenous leukemia (CML) treated with 400 mg/day imatinib demonstrate very good survival rates (> 80% 5-year survival).

### What these studies showed

- A Phase III comparison of imatinib 400 mg/day vs 800 mg/day in the TOPS study showed faster achievement of major molecular response (MMR) with the 800-mg/day dose, but similar rates of complete cytogenetic response (CCR) at 12 months.
- A randomized Phase II study of the TKI dasatinib given at doses of 100 mg/day or 50 mg twice daily, showed rapid achievement of CCR in a very high proportion of patients with previously untreated chronic-phase CML, with a favourable toxicity profile.
- An open-label Phase II study of the TKI nilotinib showed faster cytogenetic and molecular responses than imatinib in a very large proportion of patients with previously untreated chronic-phase CML, with a manageable toxicity profile.

### Next steps

- Results of an ongoing study will determine whether the standard starting dose of imatinib should change from 400 mg to 800 mg per day for this population.
- The promising early results for the newer TKIs dasatinib and nilotinib need to be confirmed in randomized controlled trials.

at 6 and 12 months make nilotinib and dasatinib attractive as initial therapy for Ph+ CML. It will be important to study these tyrosine kinase inhibitors in randomized controlled study environments similar to the NCIC CMI trial (NCT00070499), which is comparing dasatinib 100 mg/day or imatinib 800 mg/day to imatinib 400 mg/day. All the cohorts have completed accrual and 1 year CCR, MMR and toxicities will be reported next year. Until we see the results, the standard practice of starting new CML patients on imatinib 400 mg/day should remain. We eagerly await the findings of this study, as it represents a “real world” test in which patients are not excluded because of age or potentially damaging characteristics, including abnormal electrocardiograms and liver function tests.

## References

1. O'Brien SG, Guilhot F, Larson RA et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *NEJM* 2003;348(11):994-1004.
2. Druker BJ, Guilhot F, O'Brien SG et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *NEJM* 2006;355(23):2408-17.
3. Turner AR, Hewitt J, Kamruzzaman A et al. A Population (Registry) Based Analysis of the Impact of Bcr-Abl Specific Tyrosine Kinase Inhibition on Survival after Diagnosis of Philadelphia Chromosome Positive Chronic Myelogenous Leukemia. ASH 2008, Abstract 3237.

## Disclosure

Dr. Turner reports receiving research support from Bristol-Myers Squibb, Novartis, Schering-Plough and Wyeth, and being on Advisory Boards of Novartis and Bristol-Myers Squibb.

## Rituximab added to standard therapy in advanced chronic lymphocytic leukemia

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Hallek M, Fingerle-Rowson G, Fink A et al. **Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia.** ASH 2008, Abstract 325.

**TRIAL SUMMARY:** The German CLL study group (GCLLSG) designed this international, open-label, randomized Phase III trial, which evaluated the efficacy and tolerability of adding rituximab to fludarabine + cyclophosphamide chemotherapy in 817 previously untreated patients with advanced chronic lymphocytic leukemia (CLL). The chemotherapy-only group (n = 409) received fludarabine 25 mg/m<sup>2</sup> on Days 1–3 plus cyclophosphamide 250 mg/m<sup>2</sup> on Days 1–3 for six 28-day cycles. The immunochemotherapy group (n = 408) received the same regimen plus rituximab 375 mg/m<sup>2</sup> on Day 0 of the first cycle and 500 mg/m<sup>2</sup> on Day 1 in cycles 2–6. At a median observation time of 25.5 months, the overall response rate in the rituximab group was significantly higher than in the non-rituximab

group (95% vs 88%, p = 0.001), and the complete response rates were 52% vs 27%, respectively (p < 0.0001). Two-year progression-free survival (PFS) rates were 76.6% vs 62.3% (p < 0.0001). Two-year overall survival (OS) showed a trend favouring rituximab (91% vs 88%; p = 0.18). The hazard ratio (HR) was 0.59 for PFS and 0.76 for OS. Patients in the rituximab group had more neutropenia and/or leukopenia but no greater incidence of severe infections. Multivariate analyses showed that age, sex, Binet stage, cumulative illness rating scale (CIRS) score and decreased renal function (creatinine clearance < 70 mL/minute) independently predicted PFS and OS. The authors concluded that rituximab added to fludarabine + cyclophosphamide may become the new standard of care for first-line treatment of CLL.

Robak T, Moiseev S, Dmoszynska A et al. **Rituximab, fludarabine, and cyclophosphamide (R-FC) prolongs progression free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized Phase III REACH Trial.** ASH 2008, Abstract LBA-1.

**TRIAL SUMMARY:** This international, open-label Phase III trial randomized 552 patients with relapsed or treatment-refractory CLL to receive either six 28-day cycles of fludarabine (25 mg/m<sup>2</sup> per day intravenously for three days + cyclophosphamide (250 mg/m<sup>2</sup> intravenously per day for three days), or the same regimen plus rituximab given intravenously just before the fludarabine + cyclophosphamide infusion, at a dosage of 375 mg/m<sup>2</sup> on the first cycle

and 500 mg/m<sup>2</sup> on the next five cycles. Patients previously treated with fludarabine + cyclophosphamide or rituximab were not eligible. After median observation of 25 months, median PFS was 10 months longer in the group receiving rituximab compared to the group not receiving it (30.6 months vs 20.6 months; p = 0.0002; HR 0.65; 95% CI 0.51–0.82). The complete response rate was higher in the rituximab group (24% vs 13%; p = 0.0007), as was the

overall response rate (70% vs 58%;  $p = 0.0034$ ). The patients receiving only fludarabine + cyclophosphamide had median OS of 53 months, and those receiving rituximab had not yet reached median OS ( $p = 0.29$ ; HR 0.83). Thirty percent of the 47 patients in the rituximab group who relapsed received rituximab again, and 49% of the 69 patients in the non-rituximab group who relapsed received rituximab subsequently. **Table 4** shows selected rates of adverse events. The authors concluded that adding rituximab to standard-dose fludarabine + cyclophosphamide chemotherapy provided significant clinical benefit, with no new or unexpected safety issues.

**COMMENTARY:** Both of these were large-scale randomized international trials comparing fludarabine + cyclophosphamide (FC) with fludarabine + cyclophosphamide + rituximab (FCR). Two patient populations were targeted. The German CLL study (CLL8) looked at previously untreated patients and REACH looked at patients with

**TABLE 4. Selected adverse events in the REACH trial of rituximab added to fludarabine + cyclophosphamide vs fludarabine + cyclophosphamide alone**

type of event	incidence in rituximab group	incidence in chemotherapy-only group
Grade 3–4 adverse events	80%	74%
overall serious adverse events	50%	48%
Grade 3–4 neutropenia and febrile neutropenia	57%	52%
thrombocytopenia	11%	9%
Grade 3–4 infections	19%	19%
Grade 3–4 anemia	2%	5%
fatal adverse events*	13%	10%

\* fatal serious adverse events were mainly due to infections, secondary neoplasms and cardiac disorders

relapsed or refractory disease. Both studies were well balanced with respect to patient characteristics including stage and prognostic factors.

Michael Hallek’s presentation at the 2008 ASH annual meeting compared the CLL8 results to those of an earlier FCR study by Keating et al of the M.D. Anderson Cancer Center, published in 2005,<sup>1</sup> which showed a similar overall response rate, 95%, vs 93% in CLL8. However, the complete remission rate in the earlier study was 70%, compared to a 52% complete response rate in CLL8. This difference was felt to be due to the higher percentage (95%) of Binet Stage B–C patients in the CLL8 trial compared to M.D. Anderson’s 72%, plus the fact that CLL8 was a multicentre trial while M.D. Anderson’s was single-institution. CLL8 showed an overall response rate of 95% for FCR vs 88% for FC and complete response of 52% vs 27%, respectively; both of these differences were statistically significant. Longer followup is hoped to demonstrate improved OS as well. More hematologic toxicity, primarily neutropenia, was seen in the FCR arm, but no statistically significant differences in documented infections were seen between the two arms.

Lower minimal residual disease (MRD) was significantly associated with improved PFS. FCR was superior to FC, as demonstrated by a lower median MRD. However, identical MRD predicted for similar PFS in patients treated with either regimen, again establishing the goal of obtaining MRD when treating patients with CLL. The CLL8 researchers concluded that FCR should be considered for physically fit patients as first-line therapy — in fact they recommended FCR as initial standard treatment for fit CLL patients.

For patients with relapsed disease who have not had prior fludarabine + cyclophosphamide combination therapy or rituximab, the REACH trial showed that FCR was superior to FC, with statistically significant improved PFS (30.6 months vs 20.6 months), increased complete response (24.3% vs 13%) and an acceptable safety profile. Unlike in

## In brief

### Already known

- A previous non-randomized study had shown that adding rituximab to standard therapy with fludarabine + cyclophosphamide in initial treatment of patients with advanced chronic lymphocytic leukemia (CLL) provided superior efficacy with acceptable toxicity.

### What these studies showed

- In both untreated patients with advanced CLL (German CLL study group CLL8, a randomized Phase III trial) and relapsed or treatment-refractory CLL (REACH, an international, open-label Phase III trial), adding rituximab to fludarabine + cyclophosphamide provided superior overall response and progression-free survival, with trends (non-statistically significant) for overall survival. Rates of adverse events were as expected and manageable.

### Next steps

- Rituximab added to fludarabine + cyclophosphamide should be standard initial treatment for physically fit patients with advanced CLL, and for patients with relapsed or refractory CLL who have not had prior exposure to this regimen.

the CLL8 study, rituximab added to FC was shown to be advantageous for Binet Stage C patients over FC alone. The patients receiving rituximab had increased hematologic toxicity, but fatal adverse events were similar in both arms. The median OS in the chemotherapy-alone group was 53 months and has not been reached in the rituximab group, with 80% of the patients still alive. It will likely take at least 8 years of followup to reach median OS in the rituximab arm. Hence this regimen was also recommended for physi-

cally fit patients with relapsed or refractory disease.

As of January, 2009, the European Medicines Agency Committee for Human Medicinal Products has given rituximab a positive recommendation for its use in combination with chemotherapy as first-line treatment for CLL.

## Reference

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## Pentostatin replacing fludarabine in early chronic lymphocytic leukemia

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Reynolds C, Di Bella N, Lyons R et al. **Phase III Trial of Fludarabine, Cyclophosphamide, and Rituximab Vs. Pentostatin, Cyclophosphamide, and Rituximab in B-Cell Chronic Lymphocytic Leukemia.** ASH 2008, Abstract 327.

**TRIAL SUMMARY:** This multicentre, community-based trial aimed to determine whether the purine analog pentostatin would provide fewer infectious complications than fludarabine in early treatment of CLL. Patients (n = 184) with previously untreated (80%) or minimally treated B cell CLL were randomized to receive either pentostatin (4 mg/m<sup>2</sup> on Day 1) + cyclophosphamide (600 mg/m<sup>2</sup> on Day 1) + rituximab (375 mg/m<sup>2</sup> on Day 1), in 21-day cycles (n = 92), or fludarabine (20 mg/m<sup>2</sup> on Days 1–5) + the same doses of rituximab and cyclophosphamide, in 28-day cycles (n = 92). In both groups the initial dose of rituximab 100 mg/m<sup>2</sup> was given on Day 8 of Cycle 1 and the remaining 275 mg/m<sup>2</sup> was given on Day 9; in five subsequent cycles the entire 375-mg/m<sup>2</sup> dose was given on Day 1. The primary endpoint was infectious complications, and secondary endpoints were

efficacy and safety outcomes.

The infection rate (defined as temperature  $\geq$  101 degrees Fahrenheit requiring antibiotics) was 33.7% in the patients receiving pentostatin vs 30.7% in those receiving fludarabine (p = 0.67). Complete remissions were seen in 7% vs 17% of patients in the pentostatin vs fludarabine groups, respectively, with overall responses of 45% vs 57.5%. The only statistically significant efficacy difference was complete response, favouring fludarabine (p = 0.04). Several Grade 3–4 treatment-related adverse events were lower in the pentostatin group, including neutropenia (57% vs 64% for pentostatin vs fludarabine, respectively), leukopenia (17% vs 33%) and thrombocytopenia (4% vs 10%). As of May 2008, 10 fludarabine and 17 pentostatin patients had died, with two of the fludarabine deaths being infection-related. Rates of treatment discontinuation were similar between the 2 groups at 27% and 28%. The authors concluded that both regimens provided benefit in CLL, but with significant toxicity, and that the 4-mg/m<sup>2</sup> dose of pentostatin did not achieve a lowered infection rate.

### In brief

#### Already known

- Substituting pentostatin for fludarabine in combination with rituximab + cyclophosphamide had appeared to confer less toxicity and equal response rates in older patients with CLL.

#### What this study showed

- This multicentre, community-based randomized trial in previously untreated or minimally treated CLL patients comparing pentostatin vs fludarabine added to cyclophosphamide + rituximab found a non-statistically significant difference in rates of complete response favouring fludarabine, and similar rates of infection and adverse events.

#### Next steps

- Continue to seek less toxic treatments for older, less fit CLL patients.

**COMMENTARY:** Pentostatin-based combination therapy was initially designed as a treatment that would confer less toxicity and equal response rates in older CLL patients compared to fludarabine — as pentostatin was believed to cause less immunosuppression than fludarabine. Although initial studies were promising,<sup>1</sup> this multicentre community-based trial with previously untreated or minimally treated CLL patients of pentostatin vs fludarabine added to cyclophosphamide + rituximab did not confirm superiority of pentostatin. Toxicity, infection rate and hospitalization were not significantly differ-

ent for the two treatment arms. And, while initial analysis found a complete response advantage for the patients receiving fludarabine compared to those receiving pentostatin, at 17% vs 7%, with further recruitment the complete response rates were no longer statistically different. A trend toward better PFS favoured fludarabine but did not reach statistical significance. Over one-quarter of patients in each arm did not complete the protocol due to adverse events. The dosing schedules also differed from the M.D. Anderson FCR regimen,<sup>1</sup> with a smaller dose of rituximab and a different

schedule for FC, obviating direct comparison to previously published data. Further study is required to design a better-tolerated but efficacious regimen for older, less fit CLL patients. A dose of 2 mg/m<sup>2</sup> would be better tolerated, although perhaps less effective.

#### Reference

1. Kay NE, Geyer SM, Call TG et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood* 2007;109(2):405-11.

## Flavopiridol in relapsed chronic lymphocytic leukemia

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T. Lin et al. **Flavopiridol (Alvocidib) induces durable responses in relapsed chronic lymphocytic leukemia (CLL) patients with high-risk cytogenetic abnormalities.** ASH 2008, Abstract 46.

**TRIAL SUMMARY:** This was a report on results of several Phase I–II studies conducted on 117 patients with relapsed CLL (n = 107) or small lymphocytic lymphoma (n = 10) treated with flavopiridol, an agent previously shown to induce p53-independent apoptosis of CLL cells in vitro. Patients received a pharmacokinetically derived dosing schedule of a 30-minute intravenous flavopiridol bolus, followed by a 4-hour continuous infusion: a number of variations of this schedule were given. Patient characteristics included 68% male, median age 60 years with 19% > 70 years and prior therapies ranging from 1 to 14 (median 4). Almost all (116 of 117) had received prior purine analog therapy, and 73% were refractory to (n = 82) or intolerant of purine analog (n = 3) therapy. Ninety-three (79%) were Rai stage III or IV and 85 (73%) had bulky lymph nodes ≥ 5 cm.

Using National Cancer Institute (NCI) 1996 Working

Group criteria, the overall response rate was 48%, including one complete response, 52 partial responses and 3 nodular partial responses. Seven responders then had reduced-intensity allogeneic stem cell transplants, and these patients were not included in the analysis. The remaining 49 responding patients had median PFS of 10 months, and 10 of these continued to be in remission at the time of the analysis with median PFS of 12 months (range 7–22.5 months). Six patients relapsed and received further flavopiridol, of whom five responded (1 complete and 4 partial responses), with median PFS of 12.5 months. The authors concluded that flavopiridol provided durable responses in heavily treated, relapsed CLL patients, including some with bulky adenopathy and poor-risk chromosomal abnormalities — allowing some patients who had not been candidates for allogeneic cell transplants to become eligible for transplant.

### In brief

#### Already known

- Flavopiridol was previously shown to have in vitro activity in CLL, inducing p53-independent apoptosis of CLL cells.
- Alemtuzumab has documented efficacy in CLL at the price of significant infectious toxicity, so alternative treatments are sought.

#### What this study showed

- These combined results of several Phase I–II studies showed a promising 48% rate of overall response.

#### Next steps

- A larger Phase II study now underway is expected to further define the role of flavopiridol.

**COMMENTARY:** Flavopiridol has been demonstrated to be an effective agent for CLL, particularly in patients with high-risk disease with del 17p. Patients with this chromosome deletion are typically resistant to alkylators (e.g. cyclophosphamide) and fludarabine. Alemtuzumab has documented efficacy in CLL patients with del 17p, but is highly immunosuppressive, with resultant potential life-threatening infectious toxicity. Hence, developing new therapies for high-risk CLL patients is a priority.

Initial studies of flavopiridol demonstrated Grade 4–5 toxicity and hyperacute tumour lysis, but with stringent monitoring, flavopiridol is now being administered successfully and researchers have moved forward with multi-centre study design. Patients require hospitalization, allopurinol, rasburicase, intense

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hydration, frequent biochemical monitoring and availability of dialysis. This aggressive supportive approach has effectively reduced the toxicity due to tumour lysis. The patients also received dexamethasone by infusion to block the effects of IL-6 release. In patients with white blood cell counts > 200,000, 60% required dialysis<sup>1</sup> and the authors recommend against using flavopiridol in such patients. In those selected for this study, the overall response rate was 48% with some durable responses. Seven patients went on to allogeneic transplant and six were able to be retreated, with further response to flavopiridol. This agent requires experience to administer safely but may be very useful in selected patients as a bridge to transplantation. Plans are underway to test flavopiridol in combination with other agents in relapsed CLL with high-risk cytogenetic abnormalities and as maintenance therapy. **CE**

## Reference

1. Byrd JC, Lin TS, Dalton JT et al. Flavopiridol administered using a pharmacologically derived schedule is associated with marked clinical efficacy in refractory, genetically high-risk chronic lymphocytic leukemia. *Blood* 2007;109(2):399-404.

## Disclosure

Dr. Larratt reports being on advisory boards of Amgen, Novartis and Roche, and receiving honoraria from Novartis and Roche.

## COMING SOON IN ONCOLOGY EXCHANGE

### Reports from the 2009 Annual Meeting of the American Society of Clinical Oncology

#### Tailoring breast cancer chemotherapy using tumour biomarkers

*Joseph Ragaz, MD*

#### Minimizing the risk of thrombosis-related complications in cancer patients

*Mary-Frances Scully, MD*

#### Priorities for improving the lives of cancer survivors

*Svetlana Ristovski-Slijepcevic, PhD*

#### Infertility in cancer patients and the McGill Fertility Study

*Zeev Rosberger, PhD*

#### Managing mucositis in oncology patients

*Debbie Saunders Bsc, DMD*

#### Improving colorectal cancer care with quality indicators

*Robin Urquhart, MSc; Eva Grunfeld, MD, DPhil*

#### Evidence-based followup of treated cancer patients — what does the literature justify?

*Malcolm Brigden, MD and Shahid Ahmed, MD*