



ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY (ASH) December 5–8, 2009, New Orleans, Louisiana

ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO): GI CANCERS SYMPOSIUM January 22–24, 2010, Orlando, Florida

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Lymphoma

FIRST-LINE TREATMENT FOR ADVANCED DISEASE

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TRIAL SUMMARY: Bendamustine plus rituximab

Rummel MJ, Niederle N, Maschmeyer G et al. Bendamustine Plus Rituximab is Superior in Respect of Progression Free Survival and CR Rate When Compared to CHOP Plus Rituximab as First-Line Treatment of Patients with Advanced Follicular, Indolent, and Mantle Cell Lymphomas: Final Results of a Randomized Phase III Study of the StiL (Study Group Indolent Lymphomas, Germany). ASH 2009, Abstract 405.

This Phase III study randomized 549 patients with advanced follicular, other indolent and mantle cell lymphomas to receive either rituximab 375 mg/m² on Day 1 plus bendamustine 90 mg/m² on Days 1 and 2 every 28 days (B-R), or cyclophosphamide + doxorubicin + vincristine + prednisone with rituximab every 21 days (CHOP-R), for a maximum of 6 cycles. The treatment groups were balanced for known risk factors, including age, stage, lactate dehydrogenase (LDH), International Prognostic Index (IPI), Follicular Lymphoma International Prognostic Index (FLIPI), bone marrow infiltration and extranodal involvement. In the B-R and CHOP-R groups, respectively, median age was 64 vs 63 years (overall range 31–83); 76.9% vs 77.5% of patients were Stage IV, 19.2% vs 18.6% were Stage III, 55% vs 56% had follicular lymphoma, 18% vs 19% had mantle cell lymphoma, and 27% vs 24% had other types of indolent lymphoma. Of the 513 patients eligible for final analysis (260 in the B-R group and 253 in the CHOP-R group), 9 could not be evaluated for response. Six cycles of treatment were delivered to 82% of the B-R patients and 86% of the CHOP-R patients.

At median followup of 32 months, the overall response

TABLE 1. Efficacy endpoints in advanced follicular, indolent and mantle cell lymphoma patients receiving bendamustine + rituximab (B-R) vs CHOP + rituximab (CHOP-R)

	B-R	CHOP-R	p-value	hazard ratio (95% CI)
Progression-free survival	54.8 months	34.8 months	p = 0.0002	0.5765 (0.4292 to 0.7683)
Event-free survival	54 months	31 months	p = 0.0002	0.6014 (0.4515 to 0.7845)
Time to next treatment	not reached	40.7 months	p = 0.0002	0.5416 (3897 to 0.7491)

(OR) rates were similar at 93.8% in the B-R and 93.5% in the CHOP-R groups, and complete response (CR) was 40.1% vs 30.8%, respectively (p = 0.0323). Table 1 shows that patients in the B-R group had better progression-free survival (PFS), event-free survival (EFS) and longer time to next treatment (TTNT). Overall survival (OS) was similar in the two groups at the time of this report, with 34 deaths in the B-R group and 33 in the CHOP-R group. Fewer serious adverse events occurred in the B-R group than in the CHOP-R group (49 vs 74); including less Grade 3–4 neutropenia (10.7% vs 46.5%; p < 0.0001) and less Grade 3–4 leukocytopenia (12.1% vs 38.2%; p < 0.0001). The authors concluded that patients receiving the combination of bendamustine and rituximab had better PFS and CR rates and tolerated treatment better compared to those receiving CHOP-R.

LANDMARKS

COMMENTARY: The current established treatment paradigm for most patients with indolent lymphoma has been a strategy of watchful waiting, reserving therapy for those with either local or systemic symptoms, established or anticipated organ compromise, or significant cytopenias. Exceptions where earlier treatment may be considered include the small cohort of patients with early-stage disease who may be treated with radiation alone with curative intent, and the treatment of patients with follicular lymphoma Grade 3B, where some clinicians favour an anthracycline-based treatment with curative intent.

Once the decision to treat a symptomatic patient with indolent lymphoma is made, there are at least two schools of thought regarding the intensity of first-line therapy. Some clinicians (including many in Canada) adopt a practice of therapeutic restraint using alkylator-based regimens, such as single-agent chlorambucil or cyclophosphamide + vincristine + prednisone with rituximab (R-CVP), or purine analog-based regimens initially, since such therapies are generally less toxic than anthracycline-based regimens. In this treatment paradigm, anthracycline-based therapy is reserved for later use, delaying more toxic therapy and extending the number of potential treatment regimens.

Other clinicians, particularly in the US and some parts of Europe, employ more intensive therapies such as anthracycline-based regimens first line because they are associated with a longer PFS and are only moderately more toxic than R-CVP. In this instance, greater value is placed on a prolonged initial disease-free interval. Many Canadian clinicians use R-CVP as first-line therapy for patients with indolent lymphoma in whom there is an indication for treatment. Robust multi-

TABLE 2. Adverse events of R-CHOP versus B-R

Adverse Events	R-CHOP	B-R	p-value
Neutropenia Grade 3+4	46.5%	10.7%	p <0.0001
Leukocytopenia	38.2%	12.1%	p <0.0001
Alopecia	62%	15%	n/a
Infectious complications	121	95	p=0.0403
Peripheral neuropathy	73	18	p <0.0001
Stomatitis	47	16	p <0.0001
Drug-associated erythematous skin reaction	23	42	p<0.0122

centre data from the landmark trial by Marcus et al¹ suggest this approach is associated with an OR rate of 81%, a CR/CR unconfirmed (CRu) rate of 41%, median disease-free survival (DFS) of 66 months and 4-year OS of 83%.

In this context of very different approaches, there has been great interest in the final analysis of the German multi-centre randomized Phase III STiL study. This study employed bendamustine, an agent of increasing interest to hematologists and medical oncologists. First synthesized in the 1960s in East Germany by Ozegowski and Krebs, it is now being broadly studied in patients with lymphoma, myeloma and epithelial malignancies, including breast cancer. A bifunctional molecule with a nitrogen mustard-class mechlorethamine group with alkylator properties similar to chlorambucil, it also has a benzimidazole ring which antagonizes purines and amino acids. While the relative contribution of these two properties to the overall activity of bendamustine is uncertain, two important clinical observations have been the paucity of cross-resistance with other alkylating agents and in vitro synergy with rituximab. Bendamustine is well tolerated, with predominantly hematologic side effects and a low propensity to cause alopecia. Interestingly, it has been associated with both tumour lysis syndrome and hemolytic anemia. Canadian investigators have figured prominently in recently published studies^{2,3} in indolent lymphoma and are particularly interested in this agent.

In the STiL study, at median followup of 32 months, the OR rate was similar in both arms (93.5% R-CHOP and 93.8% in B-R) but there was a significantly higher CR rate in the experimental arm (30.8% with R-CHOP and 40.1% for B-R; p=0.03). Median PFS, EFS and TTT were also significantly longer in the B-R.

Strikingly, while B-R was associated with better efficacy, it was also associated with less toxicity over the period of the study duration: there were more adverse effects in the R-CHOP group, except for drug-associated erythematous skin reactions such as urticaria and rash. (Table 2)

This is a large trial in patients with various subtypes of indolent lymphoma with reasonable median followup. How will it change practice for Canadian clinicians? The STiL

IN BRIEF

Already known

- Bendamustine plus rituximab (B-R) showed promise in the treatment of relapsed/refractory indolent or mantle cell lymphomas in two previous Phase II studies; further data was required to confirm the role of B-R.

What this study shows

- B-R improves PFS and CR rates compared to CHOP plus rituximab (CHOP-R).
- B-R was better tolerated than CHOP-R (significantly less neutropenia Grade 3 + 4 and less leukocytopenia)
- B-R has the potential to become standard first-line treatment for patients with follicular, mantle and indolent lymphomas.

Next steps

- Further followup of this study will shed light on OS.
- Await further studies on the use of bendamustine in aggressive-histology lymphoma, and data on effect of bendamustine on stem cells, and morbidity and mortality of subsequent autologous and allogeneic transplantation.

study demonstrates that B-R prolongs PFS and other measures of disease control compared to R-CHOP in first-line therapy of indolent lymphoma, and the combination of B-R appears to achieve this with a more favourable adverse effects profile. However, since many Canadian clinicians may not routinely use R-CHOP in first-line therapy of indolent lymphoma, the trial may not directly address current practice. Since the study describes results in first-line therapy that favour the use of B-R over R-CHOP, clinicians may infer that B-R is a highly effective therapy in indolent lymphoma. They may also infer that B-R is likely to represent an appropriate alternative to anthracycline or purine analog-based therapy in relapsed or refractory disease. Whether these data alone are sufficient to persuade patients and clinicians to adopt B-R instead of R-CVP in the first-line therapy of patients with indolent lymphoma who have an indication for treatment remains to be seen.

In considering the generalizability of the results of Rummell et al, it is important to consider whether the study population was representative of typical patients with indolent lymphoma who require therapy in Canadian clinics. This is a particularly important consideration in indolent lymphoma, where tremendous disease heterogeneity is only partly accounted for by prognostic factors described in the FLIPI index. The study population in the Rummell study is large with reasonable followup. The median age of patients on the trial (63-64 years) is a decade older than those of the Marcus trial (median age 52-53 years). There were approximately 75% of patients with Stage IV disease in the Rum-

mell study whereas 70% had Stage IV disease in the Marcus trial. The study population appears very representative of patients with indolent lymphoma who require therapy.

In summary, the results of using B-R in first-line therapy of indolent lymphoma are impressive and they come from a large, robust and representative clinical trial. Further followup of this study, particularly with respect to the effect of this therapy on OS, will be important, as will further followup with respect to late side effects of therapy. Current studies examining the role of bendamustine in aggressive-histology lymphoma and data about the effects of bendamustine on both autologous stem cell collection and the morbidity and mortality of subsequent autologous and allogeneic transplantation are also eagerly awaited. Clinicians must consider when to employ bendamustine-based regimens in their treatment of patients with indolent lymphoma. Given there are currently 32 clinical trials registered at Clinicaltrials.gov that are studying the effects of bendamustine in patients with lymphoproliferative disorders, we can expect more data about this agent in the future.

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Multiple myeloma

OUTCOME IMPROVEMENTS USING COMBINATION REGIMENS IN OLDER PATIENTS

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TRIAL SUMMARY: Treatment of older patients

Mateos M, MD, Oriol A, Martinez J et al. A Prospective, Multicenter, Randomized, Trial of Bortezomib/Melphalan/Prednisone (VMP) Versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with Bortezomib/Thalidomide (VT) Versus Bortezomib/Prednisone (VP) in Elderly Untreated Patients with Multiple Myeloma Older Than 65 Years. ASH 2010, Abstract 3.

This Phase III trial by the Spanish Myeloma Group randomized 260 multiple myeloma (MM) patients who were 65 years and older, of whom 253 were evaluable for response to induction, to receive induction therapy of either bortezomib + melphalan + prednisone (VMP; n = 125) or bortezomib + thalidomide + prednisone (VPT; n = 128), followed by another randomization to maintenance therapy for up to three years with either bortezomib + thalidomide (VT) or bortezomib + prednisone (VP). The dosages in the VMP group were bortezomib 1.3 mg/m² twice per week

TABLE 3. VMP vs VTP at 22 months followup

Median followup (22 months)	VMP (n=125)	VTP (n=128)
2-year time to progression	75%	70%
Progression-free survival	71%	61%
Overall survival	81%	84%

for one 6-week cycle followed by once weekly for five 5-week cycles, plus oral melphalan 9 mg/m² and prednisone 60 mg/m² once daily on Days 1-4 of each cycle. Patients in the VTP group received the same doses of bortezomib and prednisone, plus thalidomide 100 mg per day. Maintenance doses were a cycle of bortezomib 1.3 mg/m² twice weekly every three months, in combination with either 50 mg thalidomide daily (VT) or 50 mg prednisone on alternate days (VP). Partial response (PR) was 81% in the VPT group and 79% in the VTP group; complete

LANDMARKS

response (CR) was 22% vs 27%, respectively. Two patients in each group had disease progression. Median followup and maintenance endpoint data is summarized in **Table 3**.

For the maintenance phase, 178 patients were randomized, of whom 143 were evaluable for efficacy. CR increased to 42% of all patients from a mean of 25% after induction therapy, with similar rates in the two arms: 46% with VT and 38% with VP.

At a median of 13 months of maintenance, a trend was seen in time to progression favouring VT (84% for VT vs 71% for VP; $p = 0.05$) but no difference in overall survival (OS) (92% for VT vs 89% for VP). In subgroup analysis, of 27 patients who had high-risk cytogenetic abnormalities at baseline — e.g. $t(4;14)$, $t(14;16)$ or $del(17p)$ — CR was similar to that of standard-risk patients: 26% with VT vs 25% with VP after induction and 42% vs 42% after maintenance. Two-year time to progression rates were similar: 74% in the high-risk vs 73% in the standard-risk groups; as was OS at two years from inclusion into the study: 77% vs 81%, respectively; however, at one year from time of ran-

domization to maintenance therapy a trend to shorter time to progression was seen in the high-risk vs the standard-risk groups (68% vs 79%), with similar OS of 90% vs 93%.

During induction, patients receiving VMP vs VTP had lower rates of \geq Grade 3 neutropenia (37% vs 21%) and fewer infections (7% vs $<1\%$), but 8.5% of those receiving VTP had \geq Grade 3 cardiac events while no cardiac events were seen in the VMP arm. Grade ≥ 3 peripheral neuropathy occurred in 5% vs 9% of patients receiving VMP vs VTP, respectively (not statistically significant). Grade ≥ 3 toxicities reported during maintenance therapy were cardiac events (2 on VT vs 1 on VP); gastrointestinal events (4 on VT vs 1 on VP), and one fatal case of sepsis in a patient on VT. The authors concluded that both VMP and VTP provided similar, high OR and CR rates but with different toxicities, that both VT and VP maintenance therapies improved response with few adverse events, and that the combination of induction plus maintenance with either regimen improves the prognosis of elderly MM patients with high-risk cytogenetic abnormalities.

COMMENTARY: The introduction of bortezomib, thalidomide and lenalidomide into the treatment of myeloma over the past decade has led to significant improvements in response rates, PFS and OS. These drugs are useful in both

younger, fitter patients and older, frailer patients. As with most anti-cancer therapies, bortezomib, thalidomide and lenalidomide initially proved themselves in patients with relapsed disease. Given the encouraging results in the relapse setting, these agents were then moved to front-line therapy. For transplant-ineligible myeloma patients, large randomized trials¹⁻³ support a backbone of old-fashioned melphalan and prednisone combined with either daily thalidomide or twice-weekly (2 weeks out of 3) bortezomib.

Current randomized trials in this population focus on optimizing the combination of agents in the first-line drug regimen, and on the use of lower intensity maintenance therapy following induction. It is hoped that by using more of our best antimyeloma drugs up front, and by incorporating these agents into maintenance therapy, we will see further improvements in outcome compared to deferring some of the treatment to the relapse setting. The potential for improvements in myeloma disease control with increased front-line therapy must be balanced against the potential for increased toxicity. For many patients, the dose-limiting toxicity with regimens containing bortezomib or thalidomide is peripheral neuropathy, which increases with cumulative drug exposure and can persist for long periods of time following discontinuation of therapy. Multidrug combinations can also lead to serious infectious, venous thrombotic or cardiac events.

In this context, there are some interesting results from the Spanish GEM05>65 trial which was presented at ASH 2009. First, the use of combination regimens incorporating weekly bortezomib allowed for prolonged use of the drug even when combined with thalidomide, another neurotoxic agent, and encouraging two-year survival rates in excess of 80% were achieved. Second, the three-drug induction regimens that included bortezomib, prednisone and thalidomide led to increased cardiac events and treatment discontinuation due to toxicity compared to melphalan, which was associated with more hematologic and infectious toxicity. Third, the adverse prognostic impact of high-risk cyto-

IN BRIEF

Already known

- Bortezomib, thalidomide and lenalidomide are front-line agents in the treatment of myeloma; these agents are associated with increased response rates, PFS and OS.

What this study showed

- Combination regimens incorporating bortezomib allowed for prolonged use of the drug even when combined with thalidomide; two-year survival rates of 80% were achieved.
- For the three-drug induction regimens that included bortezomib and prednisone, thalidomide resulted in treatment discontinuation due to toxicity more often than melphalan.
- The adverse prognostic impact of high-risk cytogenetics was not evident; current methods of risk stratification may not apply to patients treated with modern therapy.

Next steps

- Longer followup is needed regarding OS in patients treated with current front-line regimens versus either standard thalidomide or bortezomib in combination with melphalan and prednisone.
- Four-drug induction regimens, lenalidomide-containing combinations, and novel agents may expand options for the treatment of myeloma.

netics was not evident in this report, suggesting that current methods of risk stratification may not apply to patients treated with modern therapy. Better estimates of the PFS and OS comparisons of the different treatments used on this trial, and the impact of these treatments on long-term outcomes in patients with high-risk myeloma cytogenetics, should come with additional followup.

The optimal use of currently available drugs in the front-line induction regimen and the role of maintenance therapy for transplant-ineligible myeloma patients remain unclear. No regimen has been proven to improve OS when compared to either standard thalidomide or bortezomib in combination with melphalan and prednisone, but longer followup is needed. Trials examining four-drug induction regimens have shown promising results; the study of lenalidomide-containing combinations and the development of promising novel agents in this population may continue to further expand our options.

The search for the “best” approach to myeloma therapy will continue. We will learn to adapt the choice of treatment to the particular characteristics of the patient, based on tumour and host genetics, comorbidities and other factors. We must continue to be guided by the appropriate interpretation of evidence from carefully conducted clinical trials.

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Colon cancer

IMPACT OF KRAS BIOMARKER IN THERAPY SELECTION

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TRIAL SUMMARY: The KRAS biomarker in metastatic CRC

Van Cutsem E, Lang I, Folprecht G et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): The influence of KRAS and BRAF biomarkers on outcome: Updated data from the CRYSTAL trial. ASCO Gastrointestinal Symposium 2010, Abstract 281.

The Phase III CRYSTAL trial randomized 1198 patients with metastatic colorectal cancer (mCRC) to receive cetuximab + FOLFIRI vs FOLFIRI alone. The FOLFIRI regimen was irinotecan 180 mg/m² + fluorouracil 400 mg/m² bolus followed by a 2400 mg/m² continuous infusion + folinic acid, every two weeks. The cetuximab initial dose was 400 mg/m² on Day 1 followed by 250 mg/m² every week.¹

Chemotherapy was continued until disease progression. This updated retrospective analysis evaluated the mutation status of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) in 1063 patients by quantitative polymerase chain reaction (PCR) performed on tumour tissue genomic DNA. As shown in **Table 4**, among the 666 patients (56%) with KRAS wild-type (normal) tumours, those who received cetuximab + FOLFIRI had significantly longer overall survival (OS) and progression-free survival (PFS), and a higher rate of overall response (OR), compared to those receiving FOLFIRI alone. Among the patients whose tumours had KRAS mutations, the differences in outcomes between the two treatments were not statistically significant. The authors concluded that, for the

TABLE 4. Outcomes in metastatic colorectal cancer patients receiving cetuximab + FOLFIRI vs FOLFIRI alone, by KRAS status

	KRAS wild-type			KRAS mutated		
	cetuximab + FOLFIRI (n = 316)	FOLFIRI (n = 350)	odds ratio (OR) or hazard ratio (HR) (95% CI) p-value	Cetuximab + FOLFIRI n = 214	FOLFIRI n = 183	odds ratio (OR) or hazard ratio (HR) (95% CI) p-value
overall survival	23.5 months	20 months	HR = 0.80 (0.67–0.95) p = 0.0093	16.2 months	16.7 months	HR = 1.04 (0.83–1.28) p = 0.7551
progression-free survival	9.9 months	8.4 months	HR = 0.70 (0.56–0.87) p = 0.0012	7.4 months	7.7 months	HR = 1.17 (0.89–1.54) p = 0.2661
best overall response	57.3%	39.7%	OR = 2.07 (1.52–2.83) p < 0.0001	31.3%	36.1%	OR = 0.82 (0.54–1.24) p = 0.3475

LANDMARKS

first time in a randomized study, the addition of a targeted agent (cetuximab) to FOLFIRI in the first-line treatment of patients with mCRC with KRAS wild-type tumours significantly improved OS compared to FOLFIRI alone. This

COMMENTARY: The CRYSTAL study randomized 1198 patients with mCRC to receive FOLFIRI or cetuximab + FOLFIRI. The primary endpoint was PFS with OS as a secondary endpoint. A total of 599 patients received cetuximab + FOLFIRI and 599 received FOLFIRI alone. The initial publication showed a statistically significant improvement in PFS (hazard ratio [HR] = 0.85) favouring the experimental arm. There was no significant difference in the OS between the two treatment groups. However, when only wild-type KRAS tumours were analyzed, the HR for PFS was 0.68 in favour of the cetuximab + FOLFIRI group. There was no OS benefit.¹

At ASCO GI, Van Cutsem et al presented the updated analysis of the CRYSTAL study for KRAS wild-type patients.² Retrospectively, 666 patients were found to be KRAS wild-type. In this subgroup the patients who received cetuximab + FOLFIRI had a significantly increased median OS (23.5 months vs 20 months, HR = 0.80, $p = 0.0093$), PFS (9.9 months vs 8.4 months, HR = 0.70, $p = 0.0012$) and overall response rate (57.3% vs 39.7%, OR = 2.07, $p < 0.0001$).

This is the first time a randomized study has shown that the addition of cetuximab to FOLFIRI in the first-line

analysis strengthens the value of KRAS mutational status as both an important biomarker for selecting mCRC patients for addition of cetuximab to treatment, and as a predictor of outcome in patients receiving cetuximab.

treatment of patients with Stage IV CRC has shown a significantly improved OS compared to FOLFIRI alone. The improvement is both statistically and clinically significant. The OR rate was also increased with the addition of cetuximab, which may have clinical applications.

Does this trial alter the current management of patients with Stage IV CRC? In Canada, the epidermal growth factor receptor (EGFR) monoclonal antibodies (MAB[s]) are indicated for KRAS wild-type Stage IV CRC patients who have progressed or are intolerant to fluoropyrimidine, irinotecan and oxaliplatin-based chemotherapy. This is based on the NCIC-CTG CO.17 trial which showed a statistically significant improved OS for patients receiving cetuximab monotherapy as third-line treatment for mCRC (9.5 vs 4.8 months, HR = 0.55).³ Based on the new data presented in this study, this indication should not change. However, the use of an EGFR MAB in first-line therapy could be considered under certain circumstances.

It has been known that the number of patients receiving second- and third-line treatment drops off significantly due to a number of factors, including patient choice, rapid progression and poor performance status. Therefore, given that the CRYSTAL study has shown a survival benefit, the use of this combination could be considered in patients in whom it is felt that there may be difficulty in receiving subsequent chemotherapy.

The increased response rate seen in this study may be of some clinical significance. In patients who have borderline resectable liver metastases, increasing the response rate may allow more patients to undergo potentially curative surgery. The recently published CELIM trial provides additional support for this concept.⁴ This was a randomized Phase II study in which 114 patients with nonresectable liver metastases were randomly assigned to receive cetuximab with either FOLFOX6 (oxaliplatin + fluorouracil + folinic acid; Group A) or FOLFIRI (Group B). A confirmed partial or complete response was noted in 68% of Group A and 57% of Group B. R0 resection was performed in 38% of the Group A patients and 30% of the of the Group B patients. A retrospective analysis of response by KRAS status showed a partial or complete response in 70% of patients with KRAS wild-type tumours. Therefore in patients with borderline resectable liver metastases, the use of cetuximab plus standard chemotherapy could have some benefit. In the absence of conclusive data, however, it must be considered an interesting but nonstandard approach.

These data as a whole support the growing body of evidence regarding the impact of KRAS status on the success of cetuximab treatment. As surgical resection is the only chance for a cure in patients, the results regarding the resection of liver metastases are intriguing and deserve further evaluation.

IN BRIEF

Already known

- The use of targeted treatments with conventional cytotoxic drugs has expanded the treatment of mCRC resulting in incremental OS gains. However, biomarker development is essential in the selection of patients likely to respond to therapy.

What this study showed

- The addition of a targeted agent (cetuximab) to FOLFIRI in the first-line treatment of mCRC with KRAS wild-type tumours significantly improved OS vs treatment with FOLFIRI alone; this improvement is both statistically and clinically relevant.
- KRAS mutational status is an important biomarker for selecting mCRC patients for the addition of cetuximab to treatment, and as a predictor of outcome in patients receiving cetuximab.

Next steps

- The use of cetuximab plus standard chemotherapy in patients with borderline resectable liver metastases warrants research because it may result in increased response rate and possibly, the opportunity for potentially curative surgery.

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RECENT ADVANCES IN ADJUVANT THERAPY

Timothy Asmis, MD, FRCPC, Medical Oncologist, Ottawa Hospital Regional Cancer Centre, Assistant Professor, University of Ottawa

TRIAL SUMMARY: Adjuvant treatment of Stage III disease

G. Haller DG, Cassidy J, Taberero J et al. Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO16968): No impact of age on disease-free survival (DFS). ASCO GI Symposium 2010, Abstract 284.

The Phase III NO16968 study randomized 1886 patients following surgery for Stage III colon cancer to receive adjuvant treatment with either XELOX (capecitabine 1000 mg/m² twice per day on Days 1–4 + oxaliplatin 130 mg/m² intravenously on Day 1, every three weeks for eight cycles); or to one of two bolus FU/LV (fluorouracil + leucovorin) regimens. At 57 months median followup, patients receiving XELOX had superior disease-free survival (DFS), the primary endpoint, at three, four and five years (Table 5). The 3-year HR for DFS favouring XELOX was 0.80 (p =

TABLE 5. Disease-free survival in the NO16968 trial of XELOX (capecitabine + oxaliplatin) vs bolus FU/LV (fluorouracil + leucovorin) at 57 months followup

	3-year DFS*	4-year DFS*	5-year DFS*
XELOX	71%	68.4%	66.1%
fluorouracil + leucovorin	67%	62.3%	59.8%

* = disease-free survival

0.0045). A DFS benefit was seen both in patients younger than 70 years (HR 0.79; 95% CI 0.66–0.94) and in those 70 years and older (HR 0.87; 95% CI 0.63–1.18) The authors concluded that the improved DFS with XELOX confirms findings from previous trials, and that the patients 70 years and older gain benefits similar to those previously shown in younger patients.^{1,2,3} OS data are pending.

COMMENTARY: CRC is a common and deadly disease in Canada. This year, the Canadian Cancer Society estimates that there will be approximately 22,000 new cases diagnosed (Canadian Cancer Statistics, 2009).⁴ Of these, approximately 40% will be Stage 3.⁵ Without adjuvant chemotherapy, Stage 3 colon cancer has a five-year mortality rate from 30–55%.⁶

Recent advances with adjuvant chemotherapy have improved these ominous figures. The backbone of adjuvant chemotherapy for resected CRC is fluoropyrimidine chemotherapy. DFS and OS rates were found to be improved with the addition of oxaliplatin in both the MOSAIC trial and NSAPB C-0722.^{2,3}

Haller and colleagues reported on a clinical study of over 1800 patients with resected Stage III colon cancer who were randomized to either standard bolus FU/LV (either Mayo 71% or RP 29%) or capecitabine and oxaliplatin (XELOX). Patients who received XELOX experienced less diarrhea, alopecia, neutropenia, febrile neutropenia and stomatitis, but more vomiting and hand-foot syndrome than those patients treated with FU/LV³. Also noted on this trial was more neurotoxicity with XELOX, attributed to the use of oxaliplatin. From the recent GI ASCO presentation, we learned that patients who received XELOX had an improved DFS when compared to FU/LV. OS data is pending. This improvement in DFS is similar to what was observed in the MOSAIC trial. However, the key differ-

ence between these studies is that the MOSAIC trial has reported an improvement in OS in patients with Stage III colon cancer who received FOLFOX. This study provided us with another treatment option for patients with resected Stage III colon cancer.

Most oncologists in Canada would agree that oxaliplatin when combined with fluoropyrimidine in the adjuvant setting is the optimal chemotherapy regimen for resected Stage III CRC. In terms of the impact on routine clinical practice in Canada, the Haller et al findings are important. The XELOX regimen has the advantages of a favourable toxicity profile, involves only 8 visits to the chemotherapy suite versus the 12 visits with FOLFOX. The XELOX regimen also involves less nursing resources, as there is no need for the 46-hour chemotherapy disconnects that are required with FOLFOX. Patients are also spared the inconvenience and discomfort of a central line. The concern with these data is that overall survival has not yet been reported. As pointed out by Schmoll at the 2009 ESMO presentation,⁷ the results of this trial in terms of DFS are similar to the MOSAIC trial. His assumption would be that the OS benefit of XELOX over FU/LV will likely be shown to be equivalent to that of FOLFOX over FU/LV with longer followup.

The appropriate endpoint for adjuvant trials is controversial. Improvements in detection of metastasis, coupled with the dramatic improvements in treatment of recurrent CRC in terms of chemotherapy and surgery has improved patient

LANDMARKS

survival following recurrence. This has decreased the association between 3-year DFS and 5-year OS.⁸ Perhaps an improvement in DFS over the previous standard therapy may be the appropriate endpoint for acceptance of a new adjuvant therapy. It will be difficult to conclude which is the optimal adjuvant therapy for resected Stage III CRC because no direct comparison of FOLFOX versus XELOX

has been made. The difference in the toxicity profile as well as patient preference regarding these regimens will help oncologists and patients decide between these two effective adjuvant therapy regimens.

Going forward, we will need to explore innovative therapies, as there is still a substantial recurrence rate, despite effective adjuvant therapy. This is especially pressing since the emerging evidence of the biologic therapies such as bevacizumab and the anti-EGFR MAb has not shown an improvement over oxaliplatin-based adjuvant chemotherapy in patients with resected CRC.

IN BRIEF

What is already known

- Adjuvant capecitabine is at least equivalent to bolus IV FU/LV for DFS and OS in Stage II colon cancer.
- Newer adjuvant regimens are not associated with significant efficacy benefits vs FU/LV in patients > 70 years (ACCENT database findings).

What this study showed

- XELOX shows superiority vs bolus FU/LV for DFS as adjuvant treatment for Stage III colon cancer.
- This study confirms the benefits of oxaliplatin + FU/LV combinations in Stage III patients in the MOSAIC and NSABP C-07 studies.
- Efficacy benefits with XELOX are maintained in patients > 70 years; this differs from the findings in the ACCENT meta-analysis and MOSAIC.

Next steps

- Trial followup is ongoing and OS data are eagerly awaited.

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Pancreatic cancer

NOVEL SCREENING TOOLS

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TRIAL SUMMARY: Early detection of pancreatic cancer

Gold DV, Goggins M, Newsome G et al. The PAM4 serum enzyme immunoassay (EIA) for detection of early-stage pancreatic carcinoma. ASCO GI symposium 2010, Abstract 135.

This study examined levels of the PAM4-antigen with a PAM4 MAb also called clivatuzumab, in the serum of 68 patients who had surgical resection of pancreatic cancer and in 19 volunteer controls, using a PAM4 enzyme immunoassay (EIA) previously shown to have detection rates of 77% sensitivity and 95% specificity. The present analysis

showed sensitivity for all stages of pancreatic cancer of 81% and specificity of 95%, compared to the healthy volunteers. In early disease, sensitivity was 62% for Stage I pancreatic cancer and 86% for Stage II. Sensitivity rates for Stage IA and IB subgroups were 54% and 75%, respectively, however the number of patients in each subgroup was small (13 and 8). Sensitivity of the assay for advanced Stage III and IV disease was 91%. The authors concluded that the PAM4-EIA can detect a high percentage of early Stage I and II pancreatic cancers, and that the assay should be evaluated for its impact on clinical management of this disease.

COMMENTARY: Pancreatic cancer is one of the most lethal malignancies. The near-universal lethality of this disease is in part explained by its late presentation, as a result of its

initial asymptomatic phase and propensity for early vascular invasion and metastases, and its generally poor response to radiotherapy and systemic chemotherapy. The few long-

term survivors of pancreatic cancer usually present with early-stage tumors. A Japanese study showed a 4-year survival rate of up to 78% after resection of pancreatic cancer less than 2 centimeters (Stage Ia),¹ suggesting that detection of pancreatic cancer at an early stage may improve the outcome. As such, early detection would clearly have a beneficial impact, however to date screening for pancreatic cancer and its precursor is not feasible in the general population because of the lack of an accurate, inexpensive and noninvasive diagnostic test for early-stage disease.

The most utilized serum tumour marker in pancreatic cancer is the Carbohydrate Antigen (CA) 19-9, an oligosaccharide (sialylated Lewis^a [sLe^a]) present within the MUC1 mucin-type glycoprotein. The reported sensitivity and specificity of CA 19-9 is in the range of 70% to 95% and 72% to 90% respectively.² Serial monitoring of CA 19-9 can be used in combination with imaging to monitor response to therapy in patients receiving chemotherapy. The level of CA 19-9, particularly post surgery with curative intent, is associated with long-term prognosis.^{3,4} However, CA 19-9 has many limitations. CA 19-9 detection is related to tumour stage^{4,5} and its accuracy in identifying early, potentially resectable, cancer is limited. For example, in a series of patients with resected small pancreatic tumours as described above, only 58% had an abnormal preoperative CA 19-9.¹ Also, CA 19-9 requires the presence of the Lewis blood antigen (a glycosyl transferase) to be expressed. Therefore, for approximately 5% of the population with Lewis-negative phenotype, CA 19-9 cannot be used as a biomarker.⁶ The specificity of CA 19-9 is also limited, as it can be modestly elevated in benign conditions including pancreatitis and cholangitis. For all these reasons, CA 19-9 is not a good screening marker for pancreatic cancer and the American Society of Clinical Oncology (ASCO) does not recommend CA 19-9 testing for screening purposes.⁷

Hence, interest in identifying novel pancreatic cancer markers remains strong. In 2006, Gold and colleagues described a new serum EIA for identification and quantification of PAM4-antigen in the serum. The assay demonstrated a sensitivity and specificity for pancreatic cancer of 77% and 95%, respectively. However, in this earlier analysis, no information on tumour size and stage of disease was available.² In the most recent study reported at ASCO GI 2010 in Orlando, Florida, Gold demonstrated sensitivity rates of 62% and 86% for early stages I and II disease, respectively. The authors concluded the PAM4-EIA can detect a high percentage of early Stage I and Stage II pancreatic cancer. While the sensitivity rates for Stage II disease are encouraging, one must question the screening utility of this assay if the sensitivity for stage I disease, the stage at which early detection is most likely to result in a curative intent resection, is only 62%. Additionally, given the relatively low prevalence of pancreatic cancer in the general population, the positive predictive value of clivatuzumab will be low, even if the specificity for this test was high. On the contrary, the sensitivity for detection of advanced, Stage III and IV pancreatic cancer, as reported in this abstract was high (91%). However, the sensitivity of CA 19-9 previously described

for advanced pancreatic cancer is comparable.⁵ The number of patients tested was also modest (68) and the results need to be validated in a larger prospective series with a heterogeneous patient pool including normal patients and those affected with diverse benign and malignant conditions including early-stage pancreatic cancer. According to the lead investigator of this abstract, such studies are planned.

In conclusion, we applaud efforts to identify tools for the early detection of pancreatic cancer. At present, this goal remains elusive and further studies of clivatuzumab as a screening marker are warranted based upon the preliminary findings of this abstract. It may also have therapeutic potential — by targeting the pancreatic cancer antigen, clivatuzumab may have cytotoxic potential if linked to a radioisotope or a cytotoxic drug for tumour delivery. Indeed, preliminary data have shown some antitumour activity of clivatuzumab⁸ and its efficacy as a therapeutic must also be studied in further clinical trials.

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IN BRIEF

Already known

- Pancreatic cancer is nearly always lethal; screening for this disease has not been feasible because of the lack of an accurate, noninvasive test for early-stage diagnosis.

What this study showed

- The PAM4-EIA marker can detect a high percentage of Stage I and Stage II pancreatic cancer, however the sensitivity for Stage I disease (when detection will most likely result in curative intent resection) is only 62%.

Next steps

- Further studies of clivatuzumab as a screening marker, and for potential antitumour benefit, are required.

Psychosocial care

EVIDENCE FOR END-OF-LIFE PLANNING

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TRIAL SUMMARY: Advanced Care Planning

Loberiza FR, Sullivan A, Matsuyama R et al. Psychological Correlates of Having Advance Care Planning in Patients with Hematological Malignancies. *ASH 2009, Abstract 72.*

Advance care planning (ACP) involves learning about, making and documenting choices that affect actions taken in a healthcare crisis. To examine the psychologic correlates of ACP, this study reviewed data from the observational Hematology Communications study, which investigated doctor-patient communication. Among 293 patients in the study, 149 (51%) had both designated a healthcare proxy and completed a living will, and were classified as having ACP. The 144 who lacked one or both were classified as not having ACP. Patients with ACP were more likely to be older (median age 56 vs 52 years), to report higher income, to be diagnosed with leukemia or myelodysplastic syndrome (MDS) and to have received prior treatment for cancer. These patients had worse prognoses as estimated by their physicians and based on known cure rates for their diseases. Thirty percent of patients with ACP discussed their plans

with physicians, 62% with families, and 8% had not discussed them with anyone. Multivariate analysis adjusted for age, diagnosis, income, prior treatment and patient's perceived life expectancy showed that those who used problem-focused rather than emotion-focused coping styles were more likely to have ACP. Problem-solving styles included: use of instrumental support, e.g. advice, assistance or information ($p < 0.001$); active coping, e.g. "doing something" ($p = 0.006$); use of emotional support, e.g. seeking moral support and discussing feelings ($p = 0.009$); making a plan of action ($p = 0.04$); and positive reframing ($p = 0.04$). Discussing plans with physicians was associated with general health ($p = 0.007$) and overall score on the physical composite 36-item short-form (SF-36; $p = 0.03$). Discussing and having ACP was not associated with measures of depression, anxiety, social support and level of denial. The authors concluded that their results suggest that patients with ACP engaged in more problem-focused coping and that they may have perceived more need for ACP because of poor prognosis. The authors recommended that efforts to promote ACP should emphasize its practical benefits.

COMMENTARY: Loberiza and colleagues have opened an opportunity to dispel the myths related to ACP and to consider ways that healthcare professionals can incorporate both the concept of ACP and the skills to talk with patients and their families about planning for end of life. In recent years, national professional associations, such as the Canadian Medical Association and Canadian Nurses Association, developed policy statements encouraging practitioners to initiate the discussion, providing opportunities for patients to make decisions prior to a crisis situation. Some practitioners might feel uncomfortable with the discussion and be reluctant to upset the patient. But as Loberiza pointed out, patients with ACP were more likely to use problem-focused strategies.

However, given the cross-sectional nature of the study, we do not know if these patients were problem solvers to begin with.


Loberiza found that discussing ACP helps patients focus on making pragmatic decisions in the context of their illness. We recognize that education and support are needed both for practitioners and for patients. From a practitioner perspective, it is important to enhance communication skills to open the dialogue in a sensitive way, listen to the perspective of the patient and family, provide clear explanations of what to consider, and facilitate decision making. From a patient perspective, emotions and issues will surface, but professionals, such as psychosocial oncology specialists, social workers and psychologists, can provide support to patients

facing end-of-life decisions. Counseling benefits patients and family members and reassures physicians and nurses that patients' emotional, psychologic, and spiritual needs are being met. One Canadian study¹ identified the determinants of end-stage renal disease patients' interest in ACP. Since the study used a qualitative approach in discussing the role of physicians as well as the views of patients and their family members, it is a valuable read.

An aspect not mentioned in the Loberiza abstract but key to ensuring a patient-centred process is patient diversity, which includes ethnicity, age, gender, sexual orientation and geography (e.g. urban vs rural dweller). In multicultural Canada, little work has been done on the role of patient race and ethnicity in biomedical outcomes,^{2,3} let alone on ACP. Literature from the US has indicated that, despite important racial and ethnic differences in terminal illness acknowledgment, religion and treatment preferences among patients with advanced cancer, none of these factors accounted for observed racial and ethnic differences in ACP.⁴ It has also been noted that efforts to improve ACP by informing patients of their terminal prognosis may not be sensitive to racial/ethnic differences for prognostic disclosure and acknowledgment.⁴ However, health literacy has been seen as a key enabler on establishing preferences for care and ACP.⁵

Work on ACP is evident in Canada and includes the BC Cancer Agency's paper on cross-cultural considerations in ACP.⁶

the Health Canada implementation guide,⁷ guidelines from Cancer Care Ontario,⁸ and the Canadian Paediatric Society position statement for ACP in pediatric populations.⁹ Yet, we are unsure if there is existing evidence to guide practice and support ACP with cancer patients across the country. The Qmentum Standards for Cancer Care and Oncology Services set by Accreditation Canada do not mention ACP.¹⁰ There are, however, several systematic reviews, guidelines and policy statements that recommend key elements of ACP for cancer patients. Some of the common elements include: making ACP a routine part of provider-patient communication; facilitating patient discussions with others, such as family and spiritual advisors; giving consideration to patient diversity; discussion of options for a range of potential patient-specific issues, such as cardiopulmonary resuscitation (CPR), do not resuscitate (DNR) and site of death; ensuring cross-discipline and cross-facility communication on ACP; and periodic reviews or revisions of ACP.^{8,11,12} Of note is the von Gunten et al article that delineates a seven-step approach to communication ensuring competency in end-of-life care.¹²

ACP is an ongoing process that requires reflection, discussion with others and the communication of decisions, with the ability to adapt as clinical status changes. It is essential that healthcare professionals engage in end-of-life planning conversations with patients and their family members, and that this approach becomes the standard of care. Furthermore, all healthcare professionals need education to support the development of communication skills in order to meet patient needs. We must also be receptive to the cultural differences of our population as we engage them in ACP. 

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IN BRIEF

Already known

- Canadian physician and nursing associations recommend healthcare practitioners discuss ACP with their patients.

What this trial showed

- Patients with ACP were more likely to cope using problem-focused rather than emotion-focused strategies.
- ACP helps patients focus on pragmatic decision making in the context of their illness.
- The practical benefits of ACP can appeal to many patients, regardless of their coping style, and should be promoted for use by healthcare clinicians.

Next steps

- Research on the role of patient diversity as well as awareness of cultural differences will play an important role in ensuring optimal ACP dialogue between healthcare practitioners and patients.

Disclosure

Dr. Couban reports research support from Genzyme, advisory board participation for Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Otsuka, Schering and Roche, and is part of the speakers' bureau for Roche. Dr. Wong reports being on advisory boards for sanofi-aventis, Roche and Bristol-Myers Squibb. Dr. Asmis reports research support from sanofi-aventis, serving as a consultant for Roche, sanofi-aventis and Bristol-Myers Squibb, and being on the advisory boards of Roche and sanofi-aventis. Esther Greene, and Drs. Thomas, Wadiwalla, Reiman, Gill and Aubin report no potential conflict of interest relevant to their articles.

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