Canadian Journal of Rural Medicine
CJRM CMR
Journal canadien de la médecine rurale

Original Article
Article original

Impact of travel distance on access to treatment and survival in patients with metastatic colorectal cancer prescribed bevacizumab plus chemotherapy

Evan Payette, BSc
College of Medicine, University of Saskatchewan, Saskatoon, Sask.

Sabuj Sarker, MSc
Department of Epidemiology and Performance Measurement, Saskatchewan Cancer Agency, Saskatoon, Sask.

Haji Chalchal, MD
Department of Medicine, University of Saskatchewan, Allan Blair Cancer Centre, Regina, Sask.

Correspondence to:
Evan Payette,
evan.payette@usask.ca

This article has been peer reviewed.

Introduction: Given Saskatchewan's size and low population density outside of city centres, many rural and remote residents have issues accessing regional oncology services. We performed a study to determine whether travel distance to cancer treatment centres affects first-line treatment accessibility and survival in patients with metastatic colorectal adenocarcinoma.
Methods: Retrospective chart review of patients with stage IV metastatic colorectal adenocarcinoma collected by the Saskatchewan Cancer Agency registry between June 1, 2009, and June 30, 2013. Patients were categorized as living within 100 km of or more than 100 km from the nearest cancer treatment centre offering bevacizumab plus first-line chemotherapy. Main outcome measures were differences in first-line treatment accessibility and overall survival estimates (calculated via the Kaplan–Meier method) between cohorts.
Results: Of the 252 included patients, 91 (36.1%) resided more than 100 km from a cancer treatment centre. Accessibility of standard single-agent and combination chemotherapy in the first-line setting, when not prescribed in conjunction with bevacizumab, was comparable between cohorts. Patients living within 100 km of a treatment centre and those living more than 100 km from a treatment centre had comparable access to bevacizumab in conjunction with first-line chemotherapy (57 [62.6%] v. 116 [72.0%] patients; $p = 0.1$) and similar median overall survival (18.1 v. 25.0 mo; $p = 0.2$).
Conclusion: Neither access to bevacizumab treatment nor survival times for metastatic colorectal adenocarcinoma were significantly different between the cohorts. This suggests that health care providers in Saskatchewan may be doing well in arranging timely access to advanced oncology centres. Future studies with a larger sample, different tumour types or changes to the definition of remoteness are indicated.

Introduction : Compte tenu de la taille de la Saskatchewan et de la faible densité de sa population hors des centres urbains, beaucoup de personnes en régions rurales et éloignées ont de la difficulté à obtenir des services d'oncologie régionaux. Nous avons mené une étude pour déterminer si la distance à parcourir pour se rendre aux centres de traitement du cancer a des répercussions sur l'accès aux traitements de première intention et sur la survie des patients atteints d'adénocarcinome colorectal métastasique.
Méthodes : Nous avons procédé à un examen rétrospectif des dossiers du registre de la Saskatchewan Cancer Agency portant sur les patients atteints d'adénocarcinome colorectal métastasique de stade IV, pour la période du 1er juin 2009 au 30 juin 2013. Nous avons réparti les patients selon 2 catégories : ceux vivant à moins de 100 km et ceux vivant à plus de 100 km du centre de traitement du cancer le plus près offrant le bévacizumab et la chimiothérapie de première intention. Nous avons utilisé comme principaux indicateurs de résultats les différences entre les cohortes au niveau de l'accès au traitement de première intention et du taux de survie global estimé (calculés d'après la méthode Kaplan–Meier).
Résultats : Sur les 252 patients de l'étude, 91 (36,1 %) habitaient à plus de 100 km d'un

centre de traitement du cancer. L'accès à une monothérapie standard et à une chimiothérapie combinée en première intention, lorsque non prescrite en même temps que le bévacizumab, était comparable entre les cohortes. Les patients vivant à moins de 100 km d'un centre de traitement et ceux vivant à plus de 100 km d'un centre de traitement avaient un accès comparable au bévacizumab associé à la chimiothérapie de première intention (57 [62,6 %] c. 116 [72,0 %] patients; p = 0,1) et un taux de survie global médian similaire (18,1 c. 25,0 mois; p = 0,2).

Conclusion : Il n'y avait aucune différence sur le plan statistique entre les cohortes pour ce qui est de l'accès au traitement de bévacizumab et de la durée de survie pour l'adénocarcinome colorectal métastasique. Ces résultats suggèrent que les professionnels de la santé de la Saskatchewan réussissent bien à prévoir l'accès rapide aux centres de traitement avancé en oncologie. D'autres études sont nécessaires au moyen d'un échantillon plus important, sur d'autres types de tumeurs ou en modifiant la définition de l'éloignement.

INTRODUCTION

Colorectal cancer is the third most common cancer in Canada.[1] In 2015, there were estimated to be 770 newly diagnosed cases and 280 deaths due to colorectal cancer in Saskatchewan.[1] Of these patients, about 15%–20% had metastatic disease on initial diagnosis.[2]

Treatment for metastatic colorectal adenocarcinoma, which is the most common histological subtype of colorectal cancer, has evolved over the past 2 decades.[3,4] The standard first-line regimens initially consisted of various arrangements of 5 chemotherapeutic agents: irinotecan, fluorouracil, folinic acid, oxaliplatin and capecitabine.[4,5] Studies evaluating these regimens showed that the median overall survival of patients ranged from about 13.4 to 16.8 months.[6–8] Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor in tumours, was approved for use in Saskatchewan as of January 2008.[4,9] According to phase III clinical trials, bevacizumab, in conjunction with combination chemotherapy, can improve median overall survival by up to 5.3 months compared to combination chemotherapy alone.[7,8,10] The challenge now is ensuring that bevacizumab plus chemotherapy is accessible to all patients with metastatic colorectal cancer living in the province.

Owing to Saskatchewan's extensive land mass and low population density outside of city centres, many rural, remote and northern residents have issues accessing regional oncology services.[11,12] Reports indicate that two-thirds of remote and northern Canadian residents live farther than 100 km away from a physician. This contributes to the poorer health status and reduced life expectancy of these populations.[13] In addition, health in these communities is affected by other modifiable and nonmodifiable conditions such as age, sex, genetics, ethnicity, socioeconomic status, level of education, types of coping behaviour, physical environment, employment opportunities and working conditions.[12,13] Despite these factors, an Australian study showed that increasing distance from place of residence to radiotherapy treatment facilities was independently associated with lower survival in patients with rectal cancer.[14] This finding may be partially attributable to the increased financial burdens, stress and time away from social supports that are often incurred by patients travelling long distances for treatment.[13]

To mitigate these distance-related determinants of health, the Saskatchewan Cancer Agency developed the Community Oncology Program of Saskatchewan in collaboration with 10 of the province's 13 health regions.[15] The program, which is coordinated by the 2 provincial tertiary cancer centres, in Regina and Saskatoon, operates in 16 rural and remote hospital-based community oncology centres.[15] At the time of the study, however, only 2 of the 16 community oncology centres had the necessary resources to provide patients with bevacizumab in conjunction with chemotherapy. This is predicted to be a major barrier to access as patients being treated with this regimen require in-hospital, supervised intravenous infusion of bevacizumab once every 2 weeks.

In this study, we used the Saskatchewan Cancer Agency registry to determine whether patients with metastatic colorectal adenocarcinoma living within 100 km of a cancer treatment centre access first-line chemotherapy plus bevacizumab more often, or have higher survival rates, than patients living farther than 100 km from any of the 4 cancer treatment centres in the province offering this therapy.

METHODS

Patients

Included patients had histologically confirmed stage IV metastatic colorectal adenocarcinoma on initial diagnosis. Other selection criteria included being a Saskatchewan resident, having a colorectal primary tumour and having received a diagnosis of metastatic

disease between June 1, 2009, and June 30, 2013. Patients were excluded if they did not receive chemotherapy in the first-line setting, received single-agent fluoropyrimidine-based chemotherapy without bevacizumab or were involved in any clinical trials.

Study design

In this observational retrospective chart review, we evaluated patients who received care from at least 1 of the 4 following Saskatchewan cancer treatment centres: 1) Allan Blair Cancer Centre, Regina, 2) Saskatoon Cancer Centre, Saskatoon, 3) Battlefords Union Hospital, North Battleford, and 4) St. Peter's Hospital, Melville.

We identified patients who met the inclusion criteria using the Saskatchewan Cancer Agency registry and pharmacy database. We obtained the electronic medical records and paper charts of these patients and devised an Excel data sheet to record manually extracted data such as first-line treatment type, whether bevacizumab was provided in a second-line setting, month/year of diagnosis of metastatic colorectal adenocarcinoma, month/year of last follow-up and month/year of death (if applicable). We categorized patients into 1 of 2 groups based on distance from the nearest of the 4 cancer treatment centres offering bevacizumab plus first-line chemotherapy: 100 km or less, or more than 100 km. We used the first 3 digits of the patient's postal code and the address of each of the cancer treatment centres to approximate the distance in kilometres. We took into account that Battlefords Union Hospital and St. Peter's Hospital started providing bevacizumab with chemotherapy for metastatic colorectal cancer in February 2011.

Statistical analysis

All analyses were completed with the use of SAS software version 9.3 (SAS Institute Inc.). We used the χ^2 test to evaluate accessibility data and the Kaplan–Meier method to complete overall survival analysis. Patient's date of death was considered an event, and the study cut-off date was May 31, 2016. We calculated overall survival from the date of diagnosis of metastatic colorectal adenocarcinoma to the date of death (or of last follow-up if the patient was alive). The log-rank test at the p value of 0.05 was considered for the comparison of equality. Since we did not have the recurrence date in the data, we used overall survival as the outcome.

Ethics approval

Approval for this study was granted by the University of Saskatchewan Biomedical Research Ethics Board.

RESULTS

Patient characteristics

A total of 306 patients met the inclusion criteria. Of the 306, 54 were excluded based on the study exclusion criteria. Thus, 252 patients with histologically confirmed metastatic colorectal adenocarcinoma who received first-line chemotherapy were included in the study. Of the 252, 161 (63.9%) were categorized as living within 100 km of 1 of the 4 cancer treatment centres, and 91 (36.1%) as living more than 100 km from a treatment centre (Fig. 1).

Accessibility

Of the 161 patients who lived within 100 km of a cancer treatment centre, 116 (72.0%) received bevacizumab plus chemotherapy as a first-line treatment (Table 1). The corresponding figure for the 91 patients who resided more than 100 km from a cancer treatment centre was 57 (62.6%), an absolute difference of 9.4 percentage points; this difference did

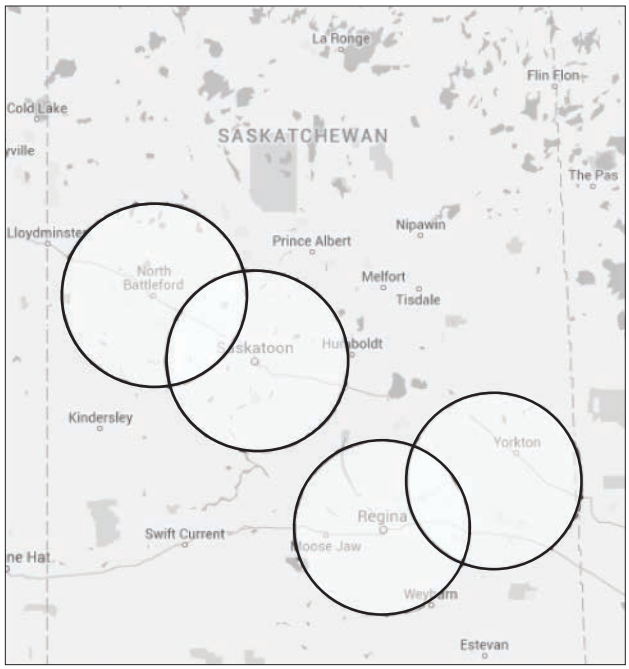

Fig. 1. Map of Saskatchewan. Four cancer treatment centres providing bevacizumab in combination with chemotherapy are indicated by circles with radius = 100 km. Left to right: Battlefords Union Hospital, North Battleford; Saskatoon Cancer Centre, Saskatoon; Allan Blair Cancer Centre, Regina; St. Peter's Hospital, Melville.

Table 1: Frequency of first-line regimens by distance to cancer treatment centre

Regimen	Distance; no. (%) of patients	
	≤ 100 km *n* = 161	> 100 km *n* = 91
CAPIRI + bevacizumab	1 (0.6)	0 (0)
CapOx*	2 (1.2)	1 (1.1)
CapOx + bevacizumab	0 (0)	2 (2.2)
FOLFIRI*	19 (11.8)	14 (15.4)
FOLFIRI + bevacizumab	94 (58.4)	48 (52.7)
FOLFOX*	19 (11.8)	15 (16.5)
FOLFOX + bevacizumab	19 (11.8)	7 (7.7)
Capecitabine*	5 (3.1)	4 (4.4)
Capecitabine + bevacizumab	2 (1.2)	0 (0)

CAPIRI = capecitabine–irinotecan, CapOx = capecitabine–oxaliplatin, FOLFIRI = folinic acid–5-FU–irinotecan, FOLFOX = folinic acid–5-FU–oxaliplatin.
*Bevacizumab administered in second-line setting.

not reach statistical significance (χ^2 = 2.39; p = 0.1). The proportions of patients in the 2 cohorts who received single-agent (capecitabine) and combination chemotherapy in the first-line setting were comparable (Table 1).

Overall survival

The median overall survival for patients who lived within 100 km of a cancer treatment centre was 25.0 months, compared to 18.1 months for those who lived more than 100 km away, a nonsignificant difference (p = 0.2) (Fig. 2).

DISCUSSION

Our results suggest that Saskatchewan patients with metastatic colorectal adenocarcinoma living more than 100 km from a cancer treatment centre offering first-line chemotherapy in conjunction with bevacizumab have comparable access to this treatment and similar median overall survival compared to patients who live within 100 km of one of these centres.

In a 2014 Australian study, the differences between rural and urban patients with metastatic colorectal cancer were also nonsignificant: 14% of rural patients and 20% of urban patients had access to first-line bevacizumab treatment, and the median overall survival was 22.0 months and 21.5 months, respectively.[16] This similarity between studies exists despite variations in regional demographic characteristics, population density and delivery of health care between the 2 countries.

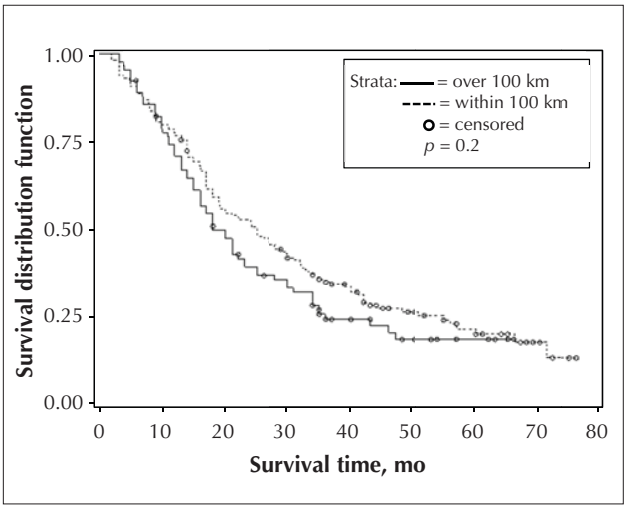

Fig. 2. Kaplan–Meier product limit overall survival estimates for patients with metastatic colorectal adenocarcinoma.

In our study, there was comparable access to standard single-agent and combination chemotherapy between the 2 cohorts. Although the median overall survival estimates and accessibility of bevacizumab plus chemotherapy as a first-line therapy were lower for the more distant cohort, the differences did not reach statistical significance. These findings suggest that oncologists, rural physicians, nurses, social workers and other health care providers may be doing well in arranging timely access to advanced oncology centres.

Strengths and limitations

Strengths of our study include the use of provincial population-level cancer registry data and estimates of travel distance based on geographic information systems and calculated from patients' partial postal codes. Limitations of the study are related to its retrospective nature, which imparts selection biases. Our failure to observe significant differences between the 2 groups may have been related to relatively small numbers, and larger studies are indicated. It is also possible that these estimates were associated with other, currently unmeasured factors. Future research using multivariate analysis examining provincial population demographic features and characteristics of patients' area of residence, which may be barriers to accessibility affecting overall survival, is necessary. Results presented in a manner that quantify the location and degree of remoteness would clarify whether a specific travel distance presents a barrier and whether any health regions require more attention and resources.

CONCLUSION

Our findings suggest that both access to bevacizumab treatment and survival times for patients with metastatic colorectal adenocarcinoma are not significantly different between those living closer to cancer treatment centres and those living farther away. This suggests that health care providers may be doing well in ensuring timely access to advanced oncology centres. Further studies with a larger sample, different tumour types or changes in the degree of remoteness are necessary.

REFERENCES

1. Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada, Provincial/Territorial Cancer Registries. *Canadian cancer statistics 2015. Special topic: predictions of the future burden of cancer in Canada*. Toronto: Canadian Cancer Society; 2015.
2. Natarajan N, Shuster TD. New agents, combinations, and opportunities in the treatment of advanced and early-stage colon cancer. *Surg Clin North Am* 2006;86:1023-43.
3. Marzouk O, Schofield J. Review of histopathological and molecular prognostic features in colorectal cancer. *Cancers (Basel)* 2011; 3:2767-810.
4. McCormack PL, Keam SJ. Bevacizumab: a review of its use in metastatic colorectal cancer. *Drugs* 2008;68:487-506.
5. Keating GM. Bevacizumab: a review of its use in advanced cancer. *Drugs* 2014;74:1891-925.
6. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013;14:1077-85.
7. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-42.
8. Guan ZZ, Xu JM, Luo RC, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. *Chin J Cancer* 2011;30:682-9.
9. Ombudsman Ontario. *Funding for Avastin across Canada*. Available: www.ombudsman.on.ca/Files/sitemedia/Documents/Investigations/SORT%20Investigations/avastcharten_1.pdf (accessed 2016 July 28).
10. Passardi A, Nanni O, Tassinari D, et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. *Ann Oncol* 2015;26:1201-7.
11. Moazzami B; Essential Skills Ontario and Saskatchewan Literacy Network. *Strengthening rural Canada: fewer and older: population and demographic crossroads in rural Saskatchewan*. 2015. Available: http://strengtheningruralcanada.ca/file/Strengthening-Rural-Canada-Fewer-and-Older-Population-and-Demographic-Crossroads-in-Saskatchewan.pdf (accessed 2016 July 28).
12. Ahmed S, Shahid RK. Disparity in cancer care: a Canadian perspective. *Curr Oncol* 2012;19:e376-82.
13. Ministerial Advisory Council on Rural Health. Rural health in rural hands: strategic directions for rural, remote, northern, and aboriginal communities. 2002. Available: http://srpc.ca/PDF/rural_hands.pdf (accessed 2016 July 28).
14. Baade PD, Dasgupta P, Aitken JF, et al. Distance to the closest radiotherapy facility and survival after a diagnosis of rectal cancer in Queensland. *Med J Aust* 2011;195:350-4.
15. Community Oncology Program of Saskatchewan. Available: www.saskcancer.ca/Default.aspx?DN=20625c14-d634-4748-9509-83d11437af7f (accessed 2016 July 28).
16. Hocking C, Broadbridge VT, Karapetis C, et al. Equivalence of outcomes for rural and metropolitan patients with metastatic colorectal cancer in South Australia. *Med J Aust* 2014;201:462-6.

Acknowledgements: The authors thank the epidemiology and research departments of the Regina Qu'Appelle Health Region and the Saskatchewan Cancer Agency for their assistance in statistical analysis and retrieval of patients' medical records.

Competing interests: None declared.

Funding: This work was supported by a grant from the Office of the Vice Dean, Research, College of Medicine, University of Saskatchewan.