Access to thalidomide for the treatment of multiple myeloma in Canada: physician behaviours and ethical implications

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ABSTRACT

Background

Multiple myeloma is an incurable malignancy. Since the late 1990s, its management has changed with the introduction of novel agents. Thalidomide, which is often called a "novel" therapy, has significantly prolonged survival in multiple myeloma and is considered worldwide to be part of standard of care in this disease. However, thalidomide is not approved in Canada, leading to problems with drug access for patients.

Methods

Our study surveyed Canadian hematologists on their thalidomide prescribing practices and difficulties with drug access. We address some of the ethical issues facing patients and their doctors who are unable to obtain or afford the drug, and who therefore resort to alternative means such as illegal importation.

Results

Of the 411 Canadian hematologists contacted, 122 completed the survey, 97 reported that they did not treat myeloma, and 192 did not respond. Assuming that all non-responders treat myeloma, our estimated overall response rate from physicians who treat this disease was 39%. Survey participants indicated that, in Canada, access to thalidomide is a major issue for physicians and myeloma patients alike, and that 81% of respondents are dissatisfied or very dissatisfied with the drug access process. Many physicians felt that the special access process for thalidomide is unduly onerous, influences treatment decisions, and invades patient privacy. We found that 20% of physicians were unaware of the legal implications of obtaining thalidomide from other countries and that at least 23% overtly or covertly support patients in obtaining the drug from a non-Health-Canada-approved source.

Conclusions

The current lack of access to thalidomide in Canada is a concerning problem for patients and health care providers dealing with myeloma. Regulatory changes at the federal level (Health Canada) need to be re-examined to promptly resolve this issue.

KEY WORDS

Thalidomide, myeloma, drug access, ethics, advocacy

1. INTRODUCTION

Multiple myeloma is a plasma-cell neoplasm with an estimated incidence in 2009 of 2200 new diagnoses and 1400 deaths in Canada [1]. This incurable cancer is characterized by multiple relapses, requiring many lines of therapy to maintain disease control. Treatment for myeloma has changed dramatically since the late 1990s and now includes several novel agents that have improved survival.

Thalidomide is a drug that was originally developed as an antiemetic for hyperemesis gravidarum, but that was removed from the market in the 1960s because of teratogenicity. Unfortunately, more than 10,000 infants worldwide were affected by devastating phocomelia as a consequence of *in utero* exposure. This situation led to the formation of victims' rights and lobby groups aimed at preventing any future *in utero* exposure to thalidomide, and tight U.S. Food and Drug Administration restrictions were thus imposed on the drug's distribution.

The first clinical trials showing efficacy with thalidomide in multiple myeloma were performed 10 years ago and led to the drug's widespread use in the setting of relapsed disease [2–8]. Since then, multiple studies have demonstrated the drug's efficacy in other settings including

- first-line treatment in combination with melphalan and prednisone (MPT) in transplant-ineligible patients [9–11], and

- maintenance therapy after autologous stem-cell transplantation (ASCT) [12–14].

Thalidomide has resulted in prolonged progression-free and overall survival in all of those settings, making the drug a standard of care for those indications. Practice guideline statements from multiple Canadian cancer care agencies, including the BC Cancer Agency, Cancer Care Ontario, and the Alberta Cancer Board, all recommend thalidomide as part of standard therapy for multiple myeloma [15–17]. Because thalidomide is effective at initial diagnosis, relapse, and maintenance, most patients with multiple myeloma will eventually be treated with the drug at some point during their illness.

Thalidomide is not a Health Canada–approved drug; it requires application to the Special Access Program (SAP) for every prescription. Celgene Corporation (Summit, NJ, U.S.A.), the American manufacturer of the drug, charges approximately US$3500 per month (assuming 200 mg daily and a 30-day supply) for its Thalomid product—a cost beyond the financial means of most patients. Celgene provides a compassionate release program, the Canadian Thalomid Access Program (CANTAP), but many patients do not qualify and are therefore unable to access the drug. Some of those patients seek alternative sources.

Thalidomide is produced generically and sold at a fraction of the Celgene cost by a number of pharmaceutical companies worldwide (for example, in England and Mexico), but Health Canada has approved only Celgene as a SAP-process source of the drug. As a result, obtaining thalidomide from sources other than Celgene is considered illegal in Canada. This situation produces an ethical dilemma for Canadian patients and physicians if the patient cannot afford the Celgene price. Should the physician suggest that the patient seek a non-Celgene "illegal" source, and if so, should the physician assist in this process? If a patient obtains the drug from a non-Celgene source, should the physician advise the patient of its illegality? Does the physician have a legal obligation to report the patient to the appropriate authorities, or at least, to stop prescribing thalidomide in this situation? Is thalidomide from the alternative sources of the same quality as that from regulated sources? How are these decisions weighed against the physician's primary responsibility to provide the best possible treatment and to serve as a patient advocate?

Clearly this issue is of importance to physicians and patients alike, as evidenced by recent publications in the lay media [18,19]. However, no published comprehensive study on the scope of the problem exists.

The purpose of the present study was to determine the thalidomide prescribing practices of Canadian hematologists who treat myeloma patients. We also wanted to identify issues related to drug access and to fully describe the physician perspective. Finally, we explored how physicians and patients deal with denial of CANTAP access to thalidomide and the ethical dilemma that this denial produces.

2. MATERIALS AND METHODS

Our study was approved by the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects. A list of Canadian hematologists was generated using a Canadian medical directory at the Web site www.mdselect.com. A search for "hematologist" generated the names of 486 physicians. Of those 486, 75 were excluded by the investigators because they were pediatric hematologists or laboratory physicians not involved directly in patient care.

In September 2009, surveys were mailed to the remaining 411 physicians. The survey included 12 multiple-choice questions about thalidomide prescribing practices and drug access issues (Table I). Space was also provided for open comments. A reminder was sent by facsimile to non-responders. To accurately determine the proportion of myeloma-treating physicians in the survey community, physician offices that did not respond to the initial request were contacted by telephone or e-mail (or both) and asked if the practice treated patients with myeloma. The survey response rate is defined as the proportion of completed surveys among the eligible (myeloma-treating) physicians that were contacted. All non-responders (those that declined to respond, or physicians who had moved) were assumed to be myeloma-treating physicians. Ineligible physicians included non-myeloma-treating hematologists and retired doctors.

Data collection was completed in January 2010. Data were analyzed as frequency distributions using the statistical software program SPSS (SPSS, Chicago, IL, U.S.A.).

3. RESULTS

Of the 411 surveys sent, 122 were returned completed. Participation was declined by 38 physicians, and 98 were ineligible (94 did not treat multiple myeloma, 3 were retired, and 1 was on maternity leave). The remaining 191 could not be reached. Assuming that all declining and non-responding physicians treat myeloma, our overall estimated response rate from physicians who treat this disease was 39%. Table II shows the distribution of responses by province.

The results of the study indicate that thalidomide use is widespread in Canada, with 90% of responding physicians reporting that they prescribe the drug. Thalidomide is prescribed mainly for recognized indications: 69% (84/122) as part of the MPT regimen, 67% (82/122) for relapsed disease, and 41% (50/122) for post–ASCT maintenance therapy. Most physicians

TABLE I Thalidomide for multiple myeloma in Canada survey

A. YOUR PRACTICE

Please enter your city and province of practice: _____

1) Do you prescribe thalidomide for the treatment of multiple myeloma?
   Yes
   No ….
   If no, please explain why: _____

2) For which patients with myeloma do you prescribe thalidomide. Circle as many as apply.
   a) First-line therapy in non-transplant-eligible patients in conjunction with other agents (e.g., melphalan, prednisone)
   b) Pre-transplant regimen in younger patients combined with another agent (e.g., dexamethasone)
   c) Maintenance therapy post transplant.
   d) Relapsed disease as a single agent or in conjunction with other agents.
   e) Only prescribed when used in a clinical trial

3) What is your first line treatment for non-transplant-eligible patients with multiple myeloma?
   a) Melphalan and prednisone (MP)
   b) Melphalan, prednisone, and thalidomide (MPT)
   c) Melphalan, prednisone, and bortezomib (MPV)
   d) Other (please enter regimen in space provided)
   _____

B. THALIDOMIDE ACCESS

4) If you prescribe thalidomide, what is your average delay between deciding to use thalidomide and the patient actually receiving thalidomide?
   a) No delay
   b) 1 month
   c) 2 months
   d) 3 months or greater

5) What proportion of your patients who are prescribed thalidomide apply to CANTAP?
   a) 0%
   b) 1%–25%
   c) 25%–50%
   d) 51%–75%
   e) >75%
   f) I don't know

6) If your patients make use of the CANTAP process, approximately what proportion of your patients are denied access through the CANTAP program?
   a) <25%
   b) 25%–50%
   c) 51%–75%
   d) >75%
   e) NA (if you do not use CANTAP)

7) How do you advise patients to obtain thalidomide if they do not qualify for compassionate coverage (CANTAP) and cannot pay out of pocket?
   a) We assist with CANTAP, and if unsuccessful, we explore alternative (non-thalidomide-based) therapies.
   b) We assist with CANTAP, and if unsuccessful, no further information is provided.
   c) We assist with CANTAP, and if unsuccessful, patient informed that non-Celgene thalidomide is an option, but no information is given on how to access it.
   d) We assist with CANTAP, and if unsuccessful, we direct patients to a support group where we expect they will learn how to obtain thalidomide from a non-Celgene source.
   e) We assist with CANTAP, and if unsuccessful, we explain to patients how to obtain thalidomide from a non-Celgene source.

TABLE I *(Continued)*

8) How do your patients who are prescribed thalidomide access it?
   a) Celgene CANTAP program
      i) Most often
      ii) Sometimes
      iii) Seldom
      iv) Never
      v) Don't know
   b) Non Celgene source (i.e., genericized thalidomide from another country e.g., Mexico or U.K.)
      i) Most often
      ii) Sometimes seldom
      iii) Never
      iv) Don't know

9) If you assist your patients in obtaining thalidomide from a non-Celgene source OR if you become aware that one of your patients has sourced thalidomide from a non-Celgene source do you:
   a) Counsel them about any additional risks posed by using a drug from a source that may not have as rigorous quality control standards as in the U.S. or Canada?
      i) Yes
      ii) No
   b) Explain the illegality of obtaining thalidomide from a non-Celgene source in Canada?
      i) Yes
      ii) No
      iii) I was unaware it was illegal

C. YOUR OPINION

10) Do you feel that it your duty as a physician to inform ALL patients who cannot access thalidomide through the CANTAP process or who cannot afford to pay out of pocket about alternative sources of thalidomide?
   a) Yes
   b) No

11) How satisfied are you with the current system for accessing thalidomide in Canada?

1	2	3	4	5
Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied

13) Please add any comments you feel relevant here.

57% (69/122) consider MPT to be first-line therapy for transplant-ineligible patients; 39% (47/122) favour the alternative regimen of melphalan, prednisone, and bortezomib.

Respondents indicated some delay in obtaining the drug: 54% (66/122) indicated an average delay of 1 month, and 34% (41/122), an average delay of 2 months. A significant number of patients were denied compassionate access to the drug through CANTAP, with 42% of respondents stating that 25% or more of their patients were refused compassionate support.

The next question asked "How do you advise patients to obtain thalidomide if they do not qualify for compassionate coverage (CANTAP) and cannot pay out of pocket?" Of respondents to this question,

- 53% chose option (a): "We assist with CANTAP and if unsuccessful we explore alternative (non-thalidomide based) therapies."
- 3% chose option (b): "We assist with CANTAP and if unsuccessful no further information is provided."
- 5% chose option (c): "We assist with CANTAP and if unsuccessful, patient informed that non-Celgene thalidomide is an option but no information is given on how to obtain it."
- 9% chose option (d): "We assist with CANTAP and if unsuccessful we direct patients to a support group where we expect they will learn how to obtain thalidomide from a non-Celgene source."
- 9% chose option (e): "We assist with CANTAP and if unsuccessful we explain to patients how to obtain thalidomide from a non-Celgene source."

TABLE II Distribution of survey respondents by province

Province	*Respondents*	
	(n)	*(%)*
Alberta	11	9.0
British Columbia	17	13.9
Manitoba	3	2.5
New Brunswick	1	0.8
Newfoundland and Labrador	1	0.8
Nova Scotia	2	1.6
Ontario	46	37.7
Prince Edward Island	1	0.8
Quebec	38	31.1
Saskatchewan	2	1.6
TOTAL	122	100

Overall, therefore, 23% of respondents to this question overtly or covertly advise patients about alternative thalidomide sources. Interestingly, 31% of respondents overall did not answer this question.

Many patients are obtaining their drug from a non-Celgene source, and 8% of the physicians reported that their patients obtain their drug in this manner "most often," 14% reported "sometimes," and 14% reported "seldom." However, 48% of physicians said that their patients "never" obtain the drug in this manner. Only 30% of physicians counselled their patients about the illegality of obtaining the drug in this manner; 20% did not know that obtaining thalidomide from a non-Celgene source was illegal in Canada; 35% counselled patients about the risks of non-Celgene thalidomide. Among survey participants, questions regarding the illegality and quality of non-Celgene product had noticeably lower response rates: 45% and 50% respectively, as compared with the other questions, which had an average 5% non-response rate (range: 1%–20%).

The next question dealt with the ethical view of the physicians about the situation—specifically, their ethical duty to provide appropriate treatment. The question said, "Do you feel it is your duty as a physician to inform all patients who cannot access thalidomide through the CANTAP process or who cannot afford to pay out of pocket about alternative sources of thalidomide?" This question received a "yes" answer from 41% of respondents.

The final question asked about satisfaction with the current system for accessing thalidomide in Canada. Answers were recorded on a Likert scale from 1 ("very dissatisfied") to 5 ("very satisfied"). The median Likert score was 1, with 54% of respondents answering 1, and 27% answering 2 ("dissatisfied").

4. DISCUSSION

Our survey had an overall response rate of approximately 39%. Responses were received from across the country; every province was included.

Although the response rate was determined to be less than 50%, the percentage response has likely been underestimated, given the assumption that all non-responding and declining-to-respond physicians actively treat multiple myeloma. Overall, the opinions given in the survey showed a degree of homogeneity, suggesting a general concern about access to thalidomide among Canadian physicians who treat myeloma. Several physicians sent us letters to the government or e-mail messages they had written advocating for patients and expressing frustration with the process.

A limitation with the survey is that responses were collected only from hematologists; we therefore have no data from other specialists who may treat myeloma (for example, general internists, medical oncologists, family physicians, and so on). The cases missed because of this focus are likely few in number, because most myeloma patients are referred to and treated at tertiary care centres by hematologists.

4.1 Standard of Care

It is clear from the study that thalidomide use is widespread in Canada. Most physicians consider thalidomide to be a standard of care for first-line therapy (in combination with melphalan and prednisone), for relapsed disease, and for post-ASCT maintenance. That finding is consistent with published data, treatment practices, and provincial guidelines. Still, a large number of physicians (39%) consider MPV (melphalan, prednisone, bortezomib) to be first-line therapy. Based on published literature [20], treatment with MPV is accepted practice, but most myeloma-treating centres worldwide use MPT as their preferred first-line choice, mainly because oral therapy is more convenient than intravenous.

There is concern that drug access may be influencing clinical practice: 53% of respondents answered that they apply for thalidomide through CANTAP and, if unsuccessful, will explore alternative (non-thalidomide-based) therapies. That finding is further supported by comments from the respondents: "The only reason we use MPV over MPT as first-line Rx is accessibility." "Don't use it [thalidomide] anymore now that Revlimid is available." "Drug access in Canada for cancer care is a huge financial issue that leads to decision-making based on access/cost instead of evidence." "Difficulty getting SAP approval and difficulty for patients who do not qualify for CANTAP support is a big problem and leads me prescribe thalidomide less frequently than I would like. Even with lenalidomide, I feel that thalidomide has a role to play in the treatment of myeloma and difficulty with access is a big problem."

4.2 Drug Access

Thalidomide is generally accepted as part of the standard of care for treating myeloma, but accessing the drug in Canada is problematic. It is currently available only through Health Canada's SAP and thus requires extensive paperwork and incurs delays. According to Health Canada, "The Special Access Program (SAP) allows practitioners to request access to drugs that are unavailable for sale in Canada. This access is limited to patients with serious or life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed, are unsuitable, or are unavailable" [21]. Clearly, the SAP is not designed for the standard day-to-day treatment of diseases such as myeloma, in which thalidomide is considered "conventional therapy." Thalidomide remains a SAP drug because Health Canada licensing requires a notice of compliance (NOC) application from the manufacturer. No manufacturer of thalidomide has yet applied for a NOC. As long as thalidomide remains an "unlicensed drug," it is up to the manufacturer to determine the drug's price.

Because Health Canada has approved only Celgene as a legitimate source of thalidomide in Canada, cost is an issue for most patients. Thalidomide's cost precludes out-of-pocket payment for most patients. Funding is not available from provincial health jurisdictions, and no private insurers cover the cost, leading patients to seek compassionate release from the Celgene CANTAP. Our study indicates that a significant proportion of patients are denied access through that mechanism.

Our pharmacy tracks all patients who apply to CANTAP and records the number granted compassionate drug supply. In 2008, 7 of 35 patients (20%) were denied access through CANTAP; in 2009, it was 12 of 40 patients (30%). This statistic does not capture patients who did not apply to CANTAP because they perceived that they would be denied funding (because of failing the "means assessment"). Furthermore, the process requires disclosure of private financial information. Comments from respondents included these: "Any program which requires a) additional paperwork b) pts to expose their financial situation is an unreasonable burden on physicians/patients." "CANTAP program is cumbersome and patients are reluctant to submit their financial records; some accept but it is an exception." "I have never been given any idea [of] their criteria for funding through CANTAP." "I think it is an invasion of privacy for patients to have to provide all the information required by CANTAP!"

The frequent refusals of compassionate thalidomide release have led many patients to seek thalidomide by alternative means. Because this drug was first introduced in the 1950s, it is manufactured by multiple companies other than Celgene, including Serral (Mexico City, Mexico) and Alan Pharmaceuticals (London, U.K.). A significant proportion (36%) of our physician respondents noted that their patients get their drug from these non-Celgene sources at least some of the time. Health Canada does not consider those firms to be legitimate sources of thalidomide and importing the drug from alternative sources is illegal in Canada. There are published data (at least for the Serral product) showing that alternative-source thalidomide has minimal pharmacokinetic differences from Celgene's Thalomid, and some studies demonstrate its anti-myeloma activity [22–28]. It should be noted, however, that these studies are limited in comparison to the large clinical trials that demonstrated the safety and efficacy of thalidomide, which used Celgene's product.

Many respondents supported the use of non-Celgene thalidomide: "Non Celgene thalidomide has been available for >10 years—Health Canada not helpful and don't care." "Need to get non-Celgene thalidomide sources recognized by Health Canada." "I have MM and have been treated with thalidomide which I had to obtain from overseas." "There is no reason we could not access another perfectly acceptable source, e.g., U.K."

Thalidomide access in Canada is currently limited in part by its SAP designation; but even if marketed, it would likely join the growing list of cancer drugs with "catastrophic" drug costs (defined as more than 3% of net household income). Patients currently not approved for compassionate supply of the drug are charged US$3500 per month, which clearly meets the criterion for "catastrophic" drug cost. A recent report by the Canadian Cancer Society defined access to cancer drugs as "the ability to obtain recommended cancer drug treatments in a timely manner and without financial hardship" [29]. Clearly, thalidomide access does not meet the criteria for "access to cancer drugs" and will remain beyond the means of many Canadians for the foreseeable future. Drugs with catastrophic costs available from alternative non-Canadian sources at a fraction of the cost will likely perpetuate the "grey market" and continue to put physicians and their patients in a difficult position.

4.3 A Question of Ethics

The use of thalidomide for multiple myeloma patients in Canada raises several ethical questions. The first has to do with the approval and funding of "orphan drugs" in Canada. Much has been written about this topic already, and our data do not contribute in any significant way to that debate. But for the practicing physician, there are other more immediate dilemmas. Prescribing thalidomide is not illegal in Canada, and therefore there is no argument about whether MPT therapy constitutes a standard of care. Physicians may ask themselves whether they should offer the treatment in the first place, particularly if they know (from experience) that a patient will not qualify, fearing that they may be providing false hope and damaging the doctor–patient

relationship. Our data suggest that some groups choose the alternative MPV because of thalidomide access issues. And when patients are denied compassionate supply of thalidomide, more than 50% of physicians choose an alternative regimen, clearly indicating that drug access is influencing their treatment choice.

Prudent physicians who recommend a thalidomide-containing regimen would discuss the question of ability to pay with their patients. However, the absence of defined and transparent criteria about who qualifies for compassionate supply hinders any open discussion and is anxiety-producing for patients already experiencing a stressful illness.

When a patient is denied access to thalidomide through CANTAP and cannot afford to pay for it out-of-pocket, the physician is confronted with a dilemma. He or she must decide whether to inform the patient about alternative, illegal sources of the drug. (We found that 20% of physicians surveyed were unaware of the illegality of obtaining thalidomide from a non-Celgene source.) Of the respondents to our survey, 41% felt that it was their duty as physicians to inform patients about alternative sources of thalidomide ("To provide the best possible treatment we should provide information or at least have the freedom to provide patients with information to obtain potentially life-prolonging therapy"). But a second question that our respondents did not address is whether they should knowingly assist the patient in obtaining illegally sourced drug: That is, if the physician knows the patient was denied access and cannot pay out of pocket, will the physician continue to provide prescriptions that will be sent to a pharmacy in Mexico? In fact, the 23% of respondents who covertly or overtly inform their patients about illegally sourced drug accepted that this second question could be affirmatively justified. But can it be?

If physicians in this position are willing to assist the patient and yet wish to claim ethical justification, they must be convinced of several facts:

- The treatment is not contrary to the standard of care, and sufficient numbers of "reasonable fellow practitioners" [30] view it as a standard of practice.
- Government regulators support the therapy in principle. (The SAP is evidence of this.)
- The patient is aware of the legal situation.
- The patient's quality of care will be significantly inferior without thalidomide.
- The alternative-source drug is both safe and efficacious.

Our data suggest that most physicians agree with the ethical justification based on the first 4 points. A minority of respondents were concerned about the assumption regarding the quality of the drug from non-Celgene sources ("[Thalidomide from Mexico] is of unknown quality"). An unregulated supply of thalidomide does raise concerns about quality control and may expose patients to undue risk.

Our data indicate that opinion diverges on the duty of physicians to assist, in any way, their multiple myeloma patients in obtaining thalidomide from an illegal source. In fact, we note that 50% of physicians chose not to respond to the questions regarding the legality or illegality of non-Celgene-sourced drug, and that 31% refused to answer how they advise patients who do not qualify for compassionate coverage. The lower response rates to these ethical questions may reflect a physician concern about the medicolegal implications of prescribing thalidomide, thereby leading to reluctance to answer the survey questions. Still, a significant portion of Canadian hematologists feel that assisting the patients is their duty. Thus, rather than put patients and doctors at risk of ethical and legal violations, the government ought to reconsider Canada's current policy position and thereby ensure that physicians can conscientiously provide the accepted standard of care to myeloma patients.

5. CONCLUSIONS

Despite being an unlicensed drug, thalidomide is widely used for the treatment of myeloma in Canada. Although viable licensed alternatives to thalidomide are available, thalidomide remains part of the accepted standard of care, and it is the drug of choice in many cases. Access to the drug is a major issue for patients and physicians, representing an excessive burden in costs and time and inappropriately influencing treatment decisions.

The current state of affairs poses an unnecessary ethical dilemma to physicians and patients alike. Physicians should not be forced to incur legal risks to deliver the high standard of care expected by the Canadian public. Patients should be spared the anxiety surrounding drug access, affordability, and (in some cases) illegal importation, so that they can focus on dealing with their illness. We propose regulatory changes by government to either

- consider regulating the importation of alternative sources of thalidomide to ensure a reliable, efficacious, and safe supply of drug, or
- provide government funding for thalidomide from the current Celgene source.

Note We understand that, in the period since the original draft of this manuscript was completed, Celgene Corporation submitted thalidomide for a NOC. An approval decision by Health Canada is pending.

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