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PRACTICE GUIDELINE

Alignment of practice guidelines with targeted-therapy drug funding policies in Ontario

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ABSTRACT

Background

We evaluated clinical practice guideline (CPG) recommendations from Cancer Care Ontario's Program in Evidence-Based Care (PEBC) for molecularly targeted systemic treatments (TTS) and subsequent funding decisions from the Ontario Ministry of Health and Long-Term Care.

Methods

We identified PEBC CPGS on TT published before June 1, 2010, and extracted information regarding the key evidence cited in support of CPG recommendations and the effect size associated with each TT. Those variables were compared with MOHLTC funding decisions as of June 2011.

Results

From 23 guidelines related to 17 TTS, we identified 43 recommendations, among which 38 (88%) endorsed TT use. Among all the recommendations, 38 (88%) were based on published key evidence, with 82% (31 of 38) being supported by meta-analyses or phase III trials. For the 38 recommendations endorsing TTS, funding was approved in 28 (74%; odds ratio related to CPG recommendation: 29.9; $p = 0.003$). We were unable to demonstrate that recommendations associated with statistically significant improvements in overall survival [OS: 14 of 16 (88%) vs. 8 of 14 (57%); $p = 0.10$] or disease- (DFS) or progression-free survival [PFS: 16 of 21 (76%) vs. 3 of 5 (60%); $p = 0.59$] were more likely to be funded than those with no significant difference. Moreover, we did not observe significant associations between funding approvals and absolute improvements of 3 months or more in OS [6 of 6 (100%) vs. 3 of 6 (50%), $p = 0.18$] or PFS [6 of 8 (75%) vs. 10 of 12 (83%), $p = 1.00$].

Conclusions

For use of TTS, most recommendations in PEBC CPGS are based on meta-analyses or phase III data, and funding decisions were strongly associated with those recommendations. Our data suggest a trend toward increased rates of funding for therapies with statistically significant improvements in OS.

KEY WORDS

Medical oncology, drug funding, health policy, clinical trials

1. INTRODUCTION

Many new anticancer treatments target molecular aspects of the particular tumour. Because these therapies have increased treatment complexity and cost, there is increasing interest in ensuring that patients receive appropriate, high-quality, evidence-based care. Synthesis of evidence into clinical practice guidelines (CPGS) has been a key tool in developing treatment policies and informing drug-funding decisions in Canada, which has a publicly-funded health care delivery system[1–3]. When making funding decisions that facilitate access to new treatments, several jurisdictions use processes that include systematic evaluations of clinical evidence[4–6]. Because molecularly targeted systemic treatments (TTS) account for most of the increase in anticancer therapy costs[7], we evaluated CPGS and drug-funding decisions for the related therapies in Ontario, Canada. Our objective was to assess the factors in evidence-based CPG recommendations that influenced subsequent funding decisions.

2. METHODS

2.1 Setting

In Canada, most new anticancer drugs are funded by universal insurance provided by provincial

governments. Once approved, residents make no direct payment for those agents, or for other institution-based services such as hospitalization, surgery, radiation therapy, or intravenous chemotherapy.

Ontario is Canada's largest province, with a population of approximately 13.4 million[8]. In 1995, Cancer Care Ontario (CCO), the province's cancer agency, established a practice guidelines initiative that evolved into the Program in Evidence-Based Care (PEBC). The PEBC uses a guideline development cycle that includes a systematic process for extracting and analyzing clinical trial data to generate evidence-based recommendations[2]. The PEBC convenes disease site groups for each cancer type, which, with centralized support, are responsible for evaluating evidence and forming CPG recommendations. Those recommendations, and other information such as pharmacoeconomic data, are submitted to drug-approval policy bodies overseen by Ontario's Ministry of Health and Long-Term Care (MOHLTC), where final policy decisions are made.

In addition to guideline documents, CCO's PEBC also prepares related series of evidence-based reports called "special reports," based on direct requests from the committee that advises the MOHLTC on drug-funding decisions. Although the special reports are systematically developed evidence-based statements, they have not completed the full guideline development cycle. For the purposes of the present study, we included both guideline document forms (that is, evidence-based guidelines and special reports), referring to them collectively as CPGs.

2.2 CPGs for TTs: Identification and Data Extraction

A single author (RR) reviewed the PEBC Web site at CCO (http://www.cancercare.on.ca) and an internal list provided the PEBC to identify all PEBC guidelines and special reports as of June 1, 2010. All CPGs related to systemic therapy were reviewed in duplicate (by RR and CMB) to identify CPGs for use of TTs (defined as nonhormonal agents that interfere with specific molecules involved with tumour growth and progression[9]) and to extract data, including tumour type, extent of disease, line of therapy, and treatment recommendations. Treatment intent was classified as curative or noncurative based on input from all study authors.

"Key evidence" is a term used by the PEBC to refer to the clinical trials data cited in the CPG short report that are most strongly associated with each recommendation. When more than one piece of key evidence was cited, a hierarchy (Figure 1) was used to identify the single data source prioritized by the CPG authors. The present study prioritized published articles over abstracts and meta-analyses or phase III trials over phase II trials. If multiple sources of key evidence remained after those criteria had been applied, the study with the largest sample size was used. For each piece of key evidence, we captured publication type, phase of the study, sample size, effect size for overall survival (OS) and disease- (DFS) or progression-free survival (PFS), and level of statistical significance associated with the foregoing differences.

2.3 Identification of Drug-Funding Decisions

In Ontario, funding for intravenous and oral chemotherapy is provided by the MOHLTC, which is advised by an independent Committee to Evaluate Drugs (CED). In 2005, an expert subcommittee was formed that included members of the CED and of CCO. The subcommittee considers CPGs developed by the PEBC, together with pharmacoeconomic and other relevant information, and then provides a recommendation to the CED to fund or not fund an agent for a specific indication. The CED reviews those recommendations and, in turn, provides its recommendation to the MOHLTC. Final MOHLTC funding decisions are available on the Web at the ministry site (http://www.health.gov.on.ca/english/providers/program/drugs/ced_rec_table.html) or at the site describing the CCO New Drug Funding Program (http://www.cancercare.on.ca/toolbox/drugs/ndfp). We reviewed both Web sites to obtain funding decisions, and we contacted CCO and MOHLTC when additional information was needed. The present study includes all drug-funding decisions reported as of June 1, 2011.

The United Kingdom also has a publicly funded health care system, and its National Institute for Health and Clinical Excellence (NICE) conducts appraisals and creates CPGs on selected topics using a mechanism that has some similarities to that used by the PEBC. For comparative purposes, we also report the TTs that were funded by NICE at the same cut-off time (So J, National Health Service Christie Trust. Personal communication).

2.4 Statistical Analysis

Descriptive statistics are used to summarize data. Hazard ratios for OS, DFS, and PFS (alone or in combination) are reported to describe the effect size for each piece of key evidence. Because not all key evidence reported hazard ratios, we used point estimates of survival distribution or median survival (or both) to derive a hazard ratio by applying a parametric model with assumptions of exponential distribution[10]. To determine the magnitude of the effect of the experimental therapy compared with the control arm in absolute terms, key evidence trials were classified as showing improvement in OS, DFS, or PFS of at least 3 months or less than 3 months. Proportions between groups were compared using the Fisher exact test[11]; differences were considered statistically significant at $p < 0.05$ (two-sided).

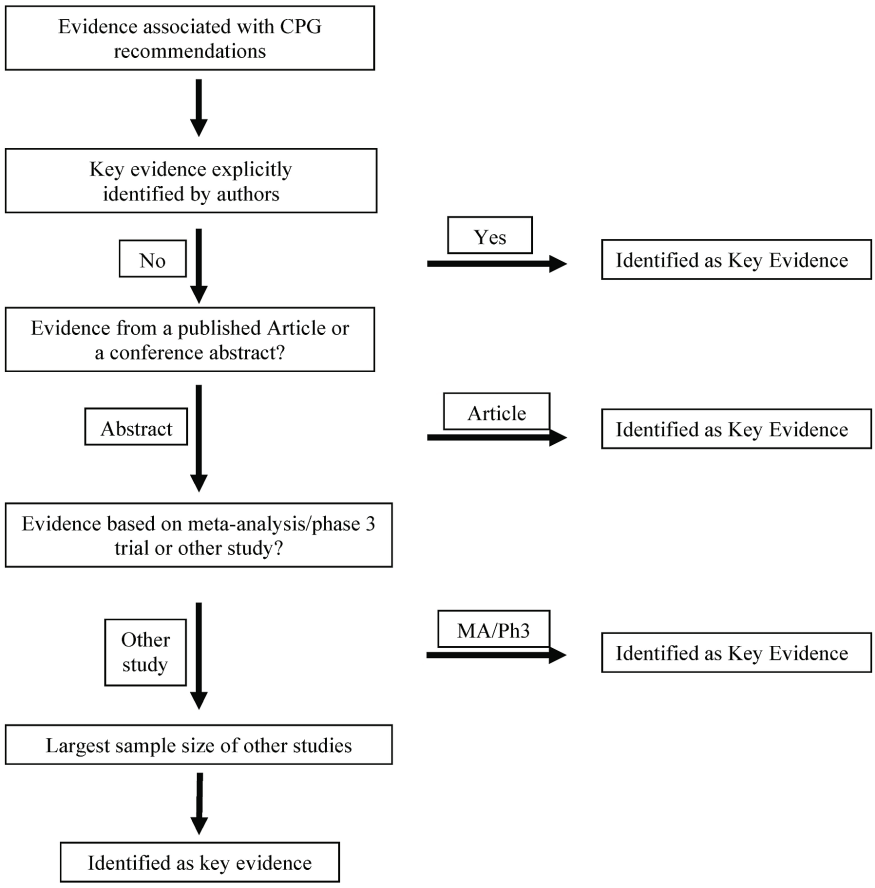

FIGURE 1 Hierarchical identification of key evidence associated with Cancer Care Ontario Program in Evidence-Based Care clinical practice guidelines (CPGs). MA = meta-analysis; Ph3 = phase III.

3. RESULTS

We identified 221 PEBC CPGs (Figure 2), including 115 that evaluated systemic therapies, of which 29 evaluated TTs. Of the latter 29 CPGs, 6 were excluded either as duplicates because of updating ($n = 2$) or because they lacked a TT recommendation ($n = 4$). The final study sample therefore included 23 TT CPGs.

3.1 Characteristics of the CPGs

The 23 CPGs in the sample covered 10 tumour sites, with hematologic malignancies accounting for 43% ($n = 10$). Most CPGs ($n = 19$, 83%) were published during 2006–2009. The TTs evaluated included bevacizumab ($n = 4$), imatinib ($n = 3$), trastuzumab ($n = 3$), alemtuzumab ($n = 2$), cetuximab ($n = 2$), dasatinib ($n = 2$), erlotinib ($n = 2$), gefitinib ($n = 2$), rituximab ($n = 2$), sorafenib ($n = 2$), sunitinib ($n = 2$), and bortezomib, everolimus, ibritumomab, panitumumab, temsirolimus, and tositumomab ($n = 1$ each).

All 23 CPGs identified relevant studies by searching MEDLINE and the conference proceedings of the American Society of Clinical Oncology. Other disease-specific conference proceedings were searched in 13 CPGs. The guidelines included an average of 14.6 studies (median: 9 studies) related to the specific TT. Evidence informing the recommendations included phase III randomized trials ($n = 23$, 100%), published meta-analyses ($n = 1$, 4%), other practice guidelines ($n = 4$, 17%), single-arm phase II trials ($n = 10$, 43%), and retrospective studies ($n = 1$, 4%). Data published in abstract form was used in 20 CPGs (87%).

3.2 Treatment Recommendations and Drug-Funding Decisions

The 23 CPGs led to 43 treatment recommendations (mean: 1.8 recommendations; median: 2 recommendations; range: 1–6 recommendations per CPG). Table I shows the characteristics of the key evidence used to determine the treatment recommendations. In 38 recommendations (88%), use of the TT was supported, and 28 recommendations (65%) cited more than one source of evidence. The mean sample size for key evidence studies was 634 patients (range: 11–5081 patients; median: 462 patients). In 38 cases (88%), the basis for the recommendation was key evidence from published articles, with the articles in 31 of those cases (82%) being reports of phase III

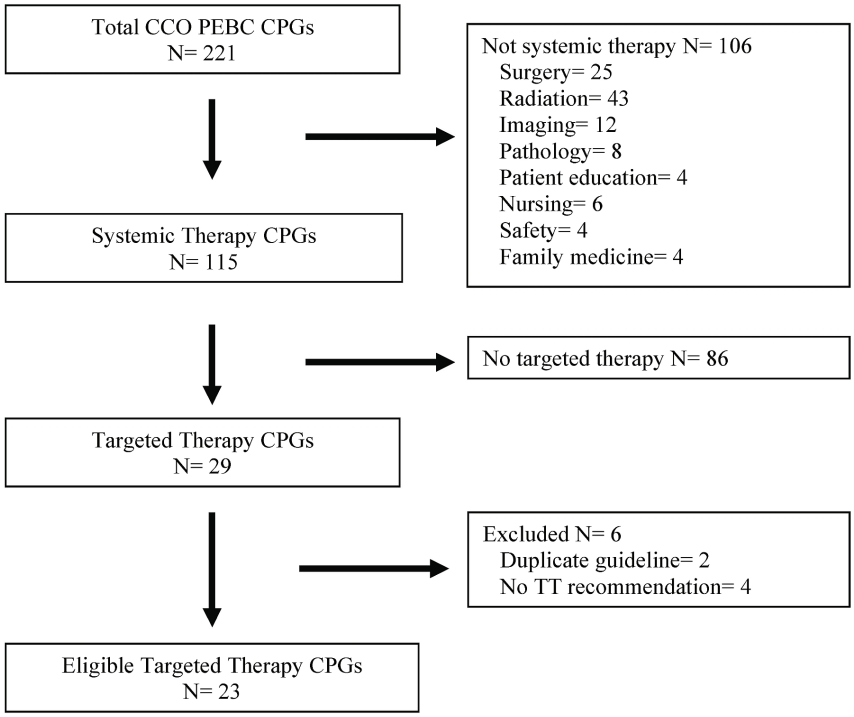

FIGURE 2 Identification of targeted therapy (TT) clinical practice guidelines (CPGs) published by Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC) to June 2011.

trials or meta-analyses; 7 recommendations (16%) were based on phase II studies. Among the 38 recommendations endorsing use of a TT, funding was approved for 28 (74%).

Table II shows the characteristics of the key evidence for recommendations that were and were not funded. Comparative measures of OS were available in 70% of cases (n = 30) and DFS or PFS in 60% (n = 26), with a statistically significant difference being detected between treatment arms in 53% (n = 16) and 81% (n = 21) of cases respectively. Absolute differences between treatment arms were reported in 12 (40%, OS) and 20 (77%, DFS/PFS) cases. An improvement of at least 3 months was observed for 6 (50%) and 8 (40%) of those cases respectively.

By univariate analysis, a CPG recommendation endorsing treatment was the only variable associated with funding approval. We did not detect differences in funding decisions based on recommendations associated with detection of a statistically significant improvement (compared with a nonsignificant improvement) in OS (14 of 16, 88% funded vs. 8 of 14, 57% funded; p = 0.10) or in DFS or PFS (16 of 21, 76% funded vs. 3 of 5, 60% funded; p = 0.59). Likewise, we did not observe an association between funding decisions and reported absolute improvements of at least 3 months (compared with less than 3 months) in median OS (6 of 6, 100% funded vs. 3 of 6, 50% funded; p = 0.18) or in DFS or PFS (6 of 8, 75% funded vs. 10 of 12, 83% funded; p = 1.00). Table III classifies treatment recommendations and corresponding effect sizes by funding status and treatment intent.

Despite access to the same data sources on the part of the PEBC and the NICE, a comparison of their recommendations showed that funding approval status was discordant between Ontario and the United Kingdom for 14 recommendations (33%, Table IV). Among the 28 therapies funded in Ontario, 15 (54%) were funded in the United Kingdom; conversely, 1 therapy not funded in Ontario was approved in the United Kingdom (gefitinib for the first-line treatment of advanced non-small-cell lung cancer—a treatment that was approved in Ontario after the June 2011 cut-off in the present study). The remaining 13 therapies are funded in Ontario but not in the United Kingdom. The only factor that predicted concordance in the funding status between Ontario and the United Kingdom was a DFS or PFS effect size that exceeded 3 months or that was statistically significant.

4. DISCUSSION

We reviewed 43 recommendations associated with 23 CPGs evaluating 17 TTs, finding that 38 recommendations (88%) supported use of the TT and that Ontario government funding was approved for 28 of them (74%). Funding approval decisions were strongly associated with CPG recommendations.

Several other important findings emerged. First, most CPG recommendations (79%) are supported by data from phase III trials. Second, among CPG

TABLE I Characteristics of clinical practice guideline recommendations and associated key evidence for targeted anticancer therapy from Cancer Care Ontario's Program in Evidence-Based Care (n = 43)

Variable	*Value*
Key evidence	
Sample size (n)	
Mean	634
Range	11–5081
Median	462
Design [n (%)]	
Article	38 (100)
Meta-analysis/phase III	31 (78)
Phase II	7 (22)
Abstract	5 (100)
Meta-analysis/phase III	3 (60)
Phase II	2 (40)
Drug recommendation and funding [n (%)]	
Recommended	
Yes	38 (88)
Funded	
Yes	28 (74)
No	10 (26)
No	5 (12)
Funded	
Yes	0 (0)
No	5 (100)
Non-funded recommendations [n (%)]	15
Reviewed, funding denied	9 (60)
No/not submitted	5 (33)
Under review	1 (7)

recommendations with key evidence describing comparative measures of OS and DFS or PFS, the survival differences were statistically significant in 53% (16 of 30) and 81% (21 of 26) of cases respectively. Third, for more than 50% of the foregoing cases, the reported absolute difference between treatment arms was less than 3 months. Finally, although absolute effect size was not found to be associated with funding-approval decisions, we did observe a trend in association between drug funding and a statistically significant improvement in OS.

In Ontario, 9 CPG treatment recommendations did not receive funding approval. Of those 9 recommendations, only 2 were related to a treatment plan associated with potentially curative intent (alemtuzumab for T-cell leukemia); both recommendations were based on single-arm phase II studies. Among the 7 recommendations associated with noncurative intent, only 1 was associated with a statistically significant benefit in OS (bevacizumab for advanced non-small-cell lung cancer); in 2 other cases, there were statistically significant improvements in PFS or time to progression (second-line trastuzumab for advanced breast cancer and tositumomab for non-Hodgkin lymphoma). The magnitude of benefit associated with the key evidence for each of those indications was modest, with median differences between the treatment arms of less than 3 months.

Two earlier studies have evaluated approval processes for new anticancer therapies in the United Kingdom and Ontario. In their review of decision-making at Christie Hospital NHS Trust (United Kingdom), Foy *et al.*[54] described funding that was based on thresholds related to effectiveness. In a related study, Martin and colleagues[55] reported that priority-setting decisions in Ontario were based largely on clinical benefit and that rationales could change with changing costs and budgets. The present comparison of funding approval status for anticancer drugs in Ontario and the United Kingdom shows that TTS were more often approved in Ontario. Given that recommendations from NICE may place greater weight on formal economic evaluations[56] and cost effectiveness, it is possible that differences in funding decisions were related to different thresholds associated with economic evaluations. Among the 13 recommendations funded in Ontario but not approved for funding by NICE (Table IV), 2 were associated with curative intent (imatinib for Philadelphia chromosome–positive acute lymphoblastic leukemia), and 1 of those 2 was based on phase III data demonstrating a significant improvement in OS. The other 11 recommendations were associated with noncurative intent. In 3 cases, statistically significant improvements in OS had been reported (temsirolimus and sorafenib for renal cell cancer and cetuximab for metastatic head-and-neck cancer). Of the remaining 8 recommendations, 6 were associated with statistically significant improvements in PFS or time to progression. Among the 9 therapies associated with statistically significant improvements in OS, PFS, or time to progression, the magnitude of the benefit was greater than 3 months in only 2 cases (temsirolimus for renal cell cancer and bortezomib for myeloma).

While not a study specific to oncology, work by Clement *et al.* recently evaluated relationships between evidence, CPGs, and drug funding decisions in three jurisdictions: the United Kingdom (NICE), the Australia (Australian Pharmaceutical Benefit Advisory Committee), and Canada (Canadian Common Drug Review)[57]. Between 2000 and 2008, NICE recommended listing for 87% of submissions compared with 50% for the Common Drug Review and 54% for the Pharmaceutical Benefit Advisory Committee. In a related study of NICE, Mason and Drummond[58] reported that, among 55 cancer therapies assessed between 2000 and 2008, 53% were ether rejected for routine use in the U.K. National Health Service (5 of 38, 13%) or restricted to a narrow set of indications (15 of 38, 39%). Those authors also observed a trend toward more negative decisions in recent years. In

TABLE II Factors associated with drug funding status for 43 recommendations for targeted therapy from Cancer Care Ontario's Program in Evidence-Based Care

Variable	*Funded*		*Odds ratio*	p *Value*
	Yes (n=28)	*No (n=15)*		
Publication status [*n* (%)]				
Article (*n*=38)	26 (68)	12 (32)	3.25	0.32
Abstract (*n*=5)	2 (40)	3 (60)		
Level of evidence [*n* (%)]				
Meta-analysis/phase III (*n*=34)	23 (68)	11 (32)	1.67	0.70
Phase II (*n*=9)	5 (56)	4 (44)		
Treatment intent [*n* (%)]				
Curative (*n*=8)	6 (86)	2 (14)	1.77	0.69
Non-curative (*n*=35)	22 (61)	13 (39)		
Disease site [*n* (%)]				
Hematology (*n*=19)	13 (68)	6 (32)	1.30	0.76
Solid tumour (*n*=24)	15 (62)	9 (38)		
Overall survival [*n* (%)]				
Significant				
Yes (*n*=16)	14 (88)	2 (12)	5.25	0.10
No (*n*=14)	8 (57)	6 (43)		
Effect size ≥ 3 months				
Yes (*n*=6)	6 (100)	0 (0)	8.75	0.18
No (*n*=6)	3 (50)	3 (50)		
Disease- or progression-free survival				
Significant				
Yes (*n*=21)	16 (76)	5 (24)	2.13	0.59
No (*n*=5)	3 (60)	2 (40)		
Effect size ≥ 3 months				
Yes (*n*=8)	6 (75)	2 (25)	0.6	1.00
No (*n*=12)	10 (83)	2 (17)		
Recommended by CPG				
Yes (*n*=38)	28 (74)	10 (26)	29.9	0.003
No (*n*=5)	0 (0)	5 (100)		

CPG = clinical practice guideline.

another report written with colleagues[59], the same authors compared cancer drug therapy approval decisions in the United States and the United Kingdom and concluded that drug coverage decisions that include processes to consider cost-effectiveness (such as those made by NICE) are associated with greater restrictions and slower times to coverage.

The present study is the first comprehensive evaluation of the relationship between evidence, CPGs, and funding approval decisions for anticancer drugs, but the results should be interpreted in the context of study limitations. Drug-funding approval processes in Ontario have recently changed. As of October 2011, a national advisory committee [the pan-Canadian Oncology Drug Review (http://www.pcodr.ca)] has begun issuing funding recommendations to participating provincial ministries of health and the existing Ontario subcommittee of the CED. Accordingly, our conclusions may not be generalizable to future funding approval processes in Ontario or to guideline programs or funding agencies in other jurisdictions. Our study may also include more specific limitations based on our hierarchical framework for identifying key evidence (including prioritizing articles over abstracts) and a relatively small sample size of TT recommendations that likely precluded an ability to identify statistically significant findings. In only a single case (sorafenib for hepatocellular carcinoma) was a published phase II study prioritized over a conference abstract of a randomized controlled trial. Furthermore, our analyses do not take into account cases in which more than one published phase III randomized controlled trial might support a TT. To be able to explore how effect size is related

TABLE III Comparison of effect size for targeted drugs identified in 43 recommendations from Cancer Care Ontario's (CCO's) Program in Evidence-Based Care

Drug	*Disease site*	*Setting*	*Line*	*Study type*	*Report*	*Recommended by CCO CPG*	*Effect size*[a]	
							OS	*DFS/EFS, PFS/TTP*
Treatment indications with funding approval in Ontario								
Curative-intent therapy								
Trastuzumab[12]	Breast	Localized	1st	Phase III	Article	Yes	Deaths: 29 vs. 37 HR: 0.78; p=NS	DFS events: 127 vs. 220 HR: 0.58; p<0.05
Cetuximab[13]	Head and neck	Locally advanced	1st	Phase III	Article	Yes	OS: 49 vs. 29.3 months HR: 0.60; p<0.05	PFS: 17.1 vs. 12.4 months HR: 0.73; p<0.05
Rituximab[14]	NHL (elderly)	Advanced	1st	Phase III	Article	Yes	2-Year OS: 70% vs. 57% HR: 0.63; p<0.05	EFS: 57% vs. 38% HR: 0.58; p<0.05
Rituximab[14]	NHL (all patients)	Advanced	1st	Phase III	Article	Yes	2-Year OS: 70% vs. 57% HR: 0.63; p<0.05	NA NA
Imatinib[15]	ALL	Primary	1st	Phase III	Article	Yes	OS: 23.5 vs. 12.3 months HR: 0.52; p<0.05	DFS: 13.7 vs. 14.5 months HR: 1.06; p=ns
Imatinib[16]	ALL	Primary	1st	Phase II	Article	Yes	NA NA	NA NA
Non-curative-intent therapy								
Trastuzumab[17]	Breast	Metastatic	1st	Phase III	Article	Yes	OS: 22.1 vs. 18.4 months HR: 0.83; p=NS	TTP: 6.9 vs. 3 months HR: 0.43; p<0.05
Bevacizumab[18]	CRC	Metastatic	1st	Phase III	Article	Yes	OS: 21.3 vs. 19.9 months HR: 0.93; p=NS	PFS: 9.4 vs. 8 months HR: 0.85; p<0.05
Cetuximab[19]	CRC	Metastatic	2nd	Phase III	Article	Yes	OS: 6.1 vs. 4.6 months HR: 0.75; p<0.05	NA NA
Panitumumab[20]	CRC	Metastatic	2nd	Phase III	Article	Yes	NA HR: 1.00[b]; p=NS	PFS: 8 vs. 7.3 wks HR: 0.91; p<0.05
Imatinib[21]	GIST	Metastatic	2nd	Phase III	Article	Yes	2-Year OS: 74% vs. 69% HR: 1.23; p=NS	PFS: 50% vs. 44% HR: 0.84; p<0.05
Sunitinib[22]	GIST	Metastatic	3rd	Phase III	Article	Yes	NA HR: 0.49[b]; p<0.05	TTP: 27.3 vs. 6.4 weeks HR: 0.23; p<0.05
Sorafenib[23]	HCC	Metastatic	1st	Phase II	Article	Yes	NA NA	NA NA
Erlotinib[24]	NSCLC	Metastatic	2nd/3rd	Phase III	Article	Yes	1-Year OS: 31 vs. 22% HR: 0.77; p<0.05	NA NA
Temsirolimus[25]	RCC	Metastatic	1st	Phase III	Article	Yes	OS: 10.9 vs. 7.3 months HR: 0.67; p<0.05	PFS: 3.8 vs. 3.7 months HR: 0.97; p=NS
Everolimus[26]	RCC	Metastatic	2nd/3rd	Phase III	Article	Yes	NA NA	PFS: 4 vs. 1.9 months HR: 0.48; p<0.05

TABLE III Continued

Drug	*Disease site*	*Setting*	*Line*	*Study type*	*Report*	*Recommended by CCO CPG*	*Effect size*[a]	
							OS	*DFS/EFS, PFS/TTP*
Sorafenib[27]	RCC	Metastatic	2nd	Phase III	Article	Yes	OS: NA HR: 0.72[b]; $p<0.05$	PFS: 5.5 vs. 2.8 months HR: 0.51; $p<0.05$
Sunitinib[28]	RCC	Metastatic	1st	Phase III	Article	Yes	OS: 26.4 vs. 21.8 months HR: 0.83; $p<0.05$	PFS: 11 vs. 5 months HR: 0.45; $p<0.05$
Cetuximab[29]	Head and neck	Metastatic	1st	Phase III	Article	Yes	OS: 10.1 vs. 7.4 months HR: 0.73; $p<0.05$	PFS: 5.6 vs. 3.3 months HR: 0.59; $p<0.05$
Imatinib[30]	CML	Chronic	2nd	Phase II	Article	Yes	NA NA	NA NA
Imatinib[31]	CML	Chronic	1st	Phase III	Article	Yes	18-Month OS: 97% vs. 95% HR: 0.59; p=NS	18-Month PFS: 92% vs. 74% HR: 0.28; $p<0.05$
Dasatinib[32]	CML	Chronic	2nd	Phase II	Article	Yes	NA NA	NA NA
Dasatinib[33]	CML	Chronic	2nd	Phase II	Article	Yes	NA NA	15-Month PFS: 93% vs. 54% HR: 0.12; $p<0.05$
Bortezomib[34]	Myeloma	Relapse	2nd	Phase III	Article	Yes	15-Month OS: 76% vs. 65% HR: 0.64; p=NS	TTP: 9.3 vs. 6.5 months HR: 0.70; p=NS
Bortezomib[35]	Myeloma	Primary	1st	Phase III	Article	Yes	2-Year OS: 84% vs. 70% HR: 0.49; p=NS	TTP: 24 vs. 16.6 months HR: 0.69; $p<0.05$
Bortezomib[36]	Myeloma	Relapse	2nd	Phase III	Article	Yes	OS: 29.8 vs. 23.7 months HR: 0.79; $p<0.05$	TTP: 6.2 vs. 3.5 months HR: 0.56; $p<0.05$
Rituximab[37]	Follicular lymphoma	Advanced	1st	Phase III	Abstract	Yes	4-Year OS: 88% vs. 72% HR: 0.39; $p<0.05$	PFS: NA HR: 0.38; $p<0.05$
Rituximab[38]	Follicular lymphoma	Advanced	1st	Phase III	Article	Yes	2-Year OS: 95% vs. 90% HR: 0.49; $p<0.05$	NA NA
Treatment indications without funding approval in Ontario								
Funding request denied								
Curative-intent therapy								
Alemtuzomab[39]	T-Cell leukemia	Primary	1st	Phase II	Article	Yes	NA NA	NA NA
Alemtuzomab[40]	T-Cell leukemia	Relapse	2nd	Phase II	Abstract	Yes	NA NA	NA NA
Non-curative-intent therapy								
Trastuzumab[41]	Breast	Metastatic	2nd	Phase III	Article	Yes	OS: 25.5 vs. 20.4 months	PFS: 8.2 vs. 5.6 months

TABLE III Continued

Drug	Disease site	Setting	Line	Study type	Report	Recommended by CCO CPG	Effect size[a]	
							OS	DFS/EFS, PFS/TTP
							HR: 0.80; p=NS	HR: 0.68; p<0.05
Bevacizumab[42]	NSCLC	Metastatic	1st	Phase III	Article	Yes	1-Year OS: 51% vs. 44%	NA
							HR: 0.82; p<0.05	NA
Gefitinib[43]	NSCLC	Metastatic	2nd	Phase III	Article	Yes	1-Year OS: 27% vs. 21%	NA
							HR: 0.84; p=NS	NA
Bortezomib[44]	Mantle cell lymphoma	Relapse	2nd	Phase II	Article	Yes	NA	NA
							NA	NA
Tositumomab[45]	NHL	Relapse	2nd	Phase III	Abstract	Yes	NA	TTP: 6.3 vs. 5.5 months
							NA	HR: 0.87; p<0.05
Ibritumomab[46]	NHL	Relapse	2nd	Phase III	Article	Yes	NA	TTP: 10.6 vs. 10.1 months
							NA	HR: 0.95; p=NS
Alemtuzumab[47]	CLL	Relapse	2nd	Phase II	Article	Yes	NA	NA
							NA	NA
Funding request not submitted (all therapies are non-curative-intent therapy)								
Bevacizumab[48]	Breast	Metastatic	2nd	Phase III	Article	No	OS: 15.1 vs. 14.5 months	PFS: 4.86 vs. 4.17 months
							HR: 0.96; p=NS	HR: 0.86; p=NS
Erlotinib[49]	NSCLC	Metastatic	1st	Phase III	Article	No	1-Year OS: 41% vs. 42%	NA
							HR: 1.03; p=NS	NA
Gefitinib[50]	NSCLC	Metastatic	1st	Phase III	Article	No	1-Year OS: 37% vs. 42%	NA
							HR: 1.15; p=NS	NA
Bevacizumab[51]	CRC	Metastatic	2nd	Phase III	Article	No	OS: 12.9 vs. 10.8 months	PFS: 7.3 vs. 4.7 months
							HR: 0.84; p<0.05	HR: 0.64; p<0.05
Bevacizumab[52]	RCC	Metastatic	1st	Meta-analysis	Article	No	NA	PFS: 8.5 vs. 5.2 months
							NA	HR: 0.61; p<0.05
Funding request under review (all therapies are non-curative-intent therapy)								
Bevacizumab[53]	Breast	Metastatic	1st	Phase III	Article	Yes	OS: 26.7 vs. 25.2 months	PFS: 11.8 vs. 5.9 months
							HR: 0.94; p=NS	HR: 0.50; p<0.05

[a] The hazard ratios shown are all derived based on point estimates reported in the clinical practice guidelines. Studies that reported median overall survival or disease- or progression-free survival for the experimental and control arms in the CCO clinical practice guideline (or the key evidence primary publication) were classified as having an absolute effect size of at least 3 months (shaded grey) or less than 3 months (shaded black).

[b] In cases without reported point estimates, the hazard ratio is the value reported in the clinical practice guideline.

CPG = clinical practice guideline; OS = overall survival; DFS = disease-free survival; EFS = event-free survival; PFS = progression-free survival; TTP = time to progression; HR = hazard ratio; NS = nonsignificant; NHL = non-Hodgkin lymphoma; NA = not available; ALL = acute lymphoblastic leukemia; CRC = colorectal cancer; GIST = gastrointestinal stromal tumour; HCC = hepatocellular carcinoma; NSCLC = non-small-cell lung cancer; RCC = renal cell cancer; CML = chronic myeloid leukemia; CLL = chronic lymphocytic leukemia.

TABLE IV Comparison of anticancer drug funding decisions for 43 clinical practice guideline recommendations in Ontario and through the U.K. National Institute for Health and Clinical Excellence (NICE)[a]

Drug	*Disease*	*Setting*	*Line*	*Drug funded by*	
				Ontario	*NICE*
Alemtuzumab					
	CLL	Relapse	2nd	No	No
	T-cell leukemia	Primary	1st	No	No
	T-cell leukemia	Relapse	2nd	No	No
Bevacizumab					
	RCC	Metastatic	1st	No	No
	CRC	Metastatic	2nd	No	No
	CRC	Metastatic	1st	Yes	No
	NSCLC	Metastatic	1st	No	No
	Breast	Metastatic	1st	No	No
	Breast	Metastatic	2nd	No	No
Bortezomib					
	Myeloma	Relapsed	2nd[b]	Yes	Yes
	Myeloma	Relapsed	2nd	Yes	No
	Myeloma	Primary	1st	Yes	No
	MCL	Relapsed	2nd	No	No
Cetuximab					
	Head-and-neck	Locally advanced	1st	Yes	Yes
	Head-and-neck	Metastatic	1st	Yes	No
	CRC	Metastatic	2nd	Yes	Yes
Dasatinib					
	CML	Chronic	2nd	Yes	No
	CML	Chronic	2nd	Yes	No
Erlotinib					
	NSCLC	Metastatic	1st	No	No
	NSCLC	Metastatic	2nd/3rd	Yes	Yes
Everolimus					
	RCC	Metastatic	2nd/3rd	Yes	No
Gefitinib					
	NSCLC	Metastatic	2nd	No	No
	NSCLC	Metastatic	1st	No	Yes
Ibritumomab					
	NHL	Relapsed	2nd	No	No
Imatinib					
	CML	Chronic	2nd	Yes	Yes
	CML	Chronic	1st	Yes	Yes
	GIST	Metastatic	2nd	Yes	Yes
	ALL	Primary	1st	Yes	No
	ALL	Primary	1st	Yes	No
Panitumumab					
	CRC	Metastatic	2nd	Yes	No
Rituximab					
	NHL	Advanced	1st	Yes	Yes
	NHL	Advanced	1st	Yes	Yes
	Follicular lymphoma	Advanced	1st	Yes	Yes
	Follicular lymphoma	Advanced	1st	Yes	Yes

TABLE IV Continued

Drug	*Disease*	*Setting*	*Line*	*Drug funded by*	
				Ontario	*NICE*
Sorafenib					
	RCC	Metastatic	2nd	Yes	No
	HCC	Metastatic	1st	Yes	No
Sunitinib					
	RCC	Metastatic	1st	Yes	Yes
	GIST	Metastatic	3rd	Yes	Yes
Temsirolimus					
	RCC	Metastatic	1st	Yes	No
Tositumomab					
	NHL	Relapsed	2nd	No	No
Trastuzumab					
	Breast	Metastatic	1st	Yes	Yes
	Breast	Localized	1st/2nd	Yes	Yes
	Breast	Metastatic	2nd	No	No

[a] Funding status as of June 1, 2011.
[b] Monotherapy.
CLL = chronic lymphocytic leukemia; RCC = renal cell carcinoma; CRC = colorectal cancer; NSCLC = non-small-cell lung cancer; MCL = mantle cell lymphoma; CML = chronic myeloid leukemia; NHL = non-Hodgkin lymphoma; GIST = gastrointestinal stromal tumour; ALL = acute lymphoblastic leukemia; HCC = hepatocellular carcinoma.

to funding decisions, we needed to identify treatment effects. We chose a 3-month threshold for that analysis because we felt that most patients and clinicians would agree that 3 months is clinically significant, and others authors have suggested the same magnitude of effect. We compared drug funding statuses between Ontario and NICE in the United Kingdom. However, in the United Kingdom, local Cancer Drug Funds can provide funding for cancer therapies that are not approved for funding by NICE. Accordingly, it is possible that, at the local level in the United Kingdom, there is less discordance in funding status for cancer therapies than our results would suggest. Finally, we did not independently evaluate pharmacoeconomic aspects of treatment, and we suspect that, given the substantial costs of many new drugs[7], pharmacoeconomic analyses, including those provided in reports by NICE and those performed but not widely reported in Ontario evaluations, may account for the differences observed.

5. CONCLUSIONS

We reviewed 23 CPGs produced by CCO's PEBC that relate to 17 targeted cancer therapies. Funding decisions were strongly associated with the evidence-based CPG recommendations. Treatments that were endorsed by CPGS, but not approved for funding in Ontario were associated with absolute median differences in time-dependent endpoints of less than 3 months. Further work is required to better understand how effect size and pharmacoeconomic factors relate to CPG recommendations and drug-funding and policy decisions.

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7. CONFLICT OF INTEREST DISCLOSURES

CMB is supported as a CCO Chair in Health Services Research. MB is director of CCO's PEBC. RMM has served as a consultant reviewer for PEBC guidelines.

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