PROPORTIONAL HAZARDS ASSUMPTION AND ITS IMPACT ON RESULTS OF COST-EFFECTIVENESS ANALYSIS

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Objectives

If proportional hazards assumption holds, Cox regression allows for estimation of treatment effect in the form of hazard ratio. However proportional hazards assumption is rarely verified. Our aim was to estimate how proportional hazards assumption may impact cost-effectiveness.

Introduction

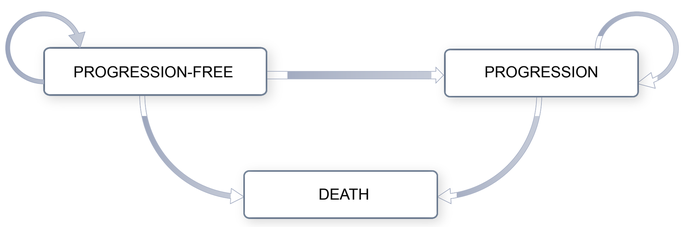
For the purposes of this analysis a review of the online clinical database Medline by PubMed was conducted. The objective of the review was to find information about using proportional hazards assumption in economic evaluation of medical interventions. One of the publications found in our data search is Guyot 2011. In that study a review of CEAs alongside trials and CEAs submitted to the National Institute for Health and Clinical Excellence Technology Appraisal program and included survival outcomes was performed. According to results of this review a common practice for CEA was to fit a parametric model to the control arm, then to apply the hazard ratio from the efficacy analysis to predict the treatment arm. Such proceedings is possible to perform in CEAs only if the proportional hazards assumption takes place. Despite this, according to Guyot 2011 [1], the proportional hazards assumption was seldom checked. In Guyot 2011 six CEAs based on evidence synthesis were analyzed. Only in two of them the proportional hazards assumption was tested. Results of CEA can vary considerably, depending on whether proportional hazards are assumed or not. We have checked the influence of proportional hazards assumption on the CEAs results.

Methods

Markov model was developed to describe cancer patients treatment. Health states distinguished in the model were: progression-free, progression and death.

10-year time horizon was assumed. The cycle length taken in the model equals 1 week. In every week patients without progression can stay in their health state or change it in case of progression or death. Patients with progression cannot move back to the Progression-Free state. They change model state only in case of death.

Figure 1. Markov model



It was assumed that utility of the health state equals 0.7 for Progression-Free and 0.4 for Progression. Death state has utility of 0. Transitions between model states are based on the time to the occurrence of the particular events based on data from clinical studies.

To find relevant clinical studies a review of the online clinical database Medline by PubMed was conducted. The only search criteria were the presentation of curves of the time to progression and overall survival and of hazard ratios between the curves. Two clinical studies were found in review performed for the purposes of this analysis. In the first study (Keinzman 2012 [2]), bisphosphonates combined with sunitinib were compared with sunitinib alone in patients with renal cell carcinoma. In the second trial (Brufsky 2012 [3]) the chemotherapy is compared to bevacizumab added to chemotherapy in selected group of patients with breast cancer. In both studies hazard ratios were calculated. In none of them proportional hazards assumption was tested.

Time to progression and overall survival were obtained from clinical trials for breast and renal cell cancer and implemented into the model on the basis of Weibull curves, fitted to data from clinical studies. All curves taken into account in the calculations are presented on the figures below.

Two analyses were performed: for renal cell cancer and breast cancer, based on data from trials found. In both analyses calculations were carried out separately with or without using given hazard parameters. In the first case a parametric model was fitted to the control arm, then hazard ratio from the relevant study was applied to predict the treatment arm. This is the most common approach in CEAs and it is correct only if proportional hazards assumption holds. In the second case a parametric model was fitted to both study arms. It was assumed that compared interventions differ only in terms of time to progression or death. All the other parameters were the same for both arms. Finally on the basis of the clinical results obtained from the model calculations and assumed differences in costs between relevant interventions conclusions about cost-effectiveness were drawn.

Results

In case of renal cell carcinoma, when time to progression differed interventions, the average time spent in progression-free state was, according to calculations under proportional hazards assumption, 1.39 years for BNS users and 0.72 for BNS non-users, thus leading to difference in QALY of 0.20. Without proportional hazards assumption BNS users have 2.01 and BNS non-users 0.72 progression-free life years, what results in 0.39 QALY gained by treatment with BNS. In case of computations without proportional hazards assumption BNS users are gaining 0.19 QALY more than they do according to calculations based on obtained hazard ratios.

When overall survival differed interventions, the average survival was, according to calculations with proportional hazards assumption, 5.17 years for BNS users and 2.65 for BNS non-users, thus leading to difference in QALY of 1.01. Without proportional hazards assumption BNS users live 5.41 and BNS non-users 2.65 years, what results in 1.11 QALY gained by treatment with BNS. In case of computations without proportional hazards assumption BNS users are gaining 0.10 QALY more than they do according to calculations based on obtained hazard ratios.

Table 1. Clinical results – renal cell carcinoma

Category		Proportional hazards assumption		
		With	Without	Difference (with vs without)
Renal cell carcinoma – differentiation of time to progression between interventions				
Progression-Free Life Years	BNS users	1.39	2.01	-0.62
	BNS non-users	0.72		-
QALY	BNS users	1.48	1.66	-0.19
	BNS non-users	1.27		-
Renal cell carcinoma – differentiation of overall survival between interventions				
Life Years	BNS users	5.17	5.41	-0.24
	BNS non-users	2.65		-
QALY	BNS users	2.29	2.38	-0.10
	BNS non-users	1.27		-

In case of breast cancer, when time to progression differed interventions, the average time spent in progression-free state was, according to calculations under proportional hazards assumption, 0.64 years for Chem + BVC vs. 0.34 for Chem, thus leading to difference in QALY of 0.09. Without proportional hazards assumption Chem + BVC patients have 0.68 and Chem patients 0.34 progression-free life years, what results in 0.10 QALY gained by treatment with Chem + BVC. In case of computations without proportional hazards assumption Chem + BVC patients are gaining 0.01 QALY more than they do according to calculations based on obtained hazard ratios.

When overall survival differed interventions, the average survival was, according to calculations with proportional hazards assumption, 1.93 years for Chem + BVC vs. 1.33 for Chem, thus leading to difference in QALY of 0.24. Without proportional hazards assumption Chem + BVC patients live 1.54 and Chem patients 1.33 years, what results in 0.09 QALY gained by treatment with Chem + BVC. In case of computations without proportional hazards assumption Chem + BVC patients are gaining 0.16 QALY less than they do according to calculations based on obtained hazard ratios.

Figure 2. Overall and progression-free survival – renal cancer (Keinzman 2012 [2])

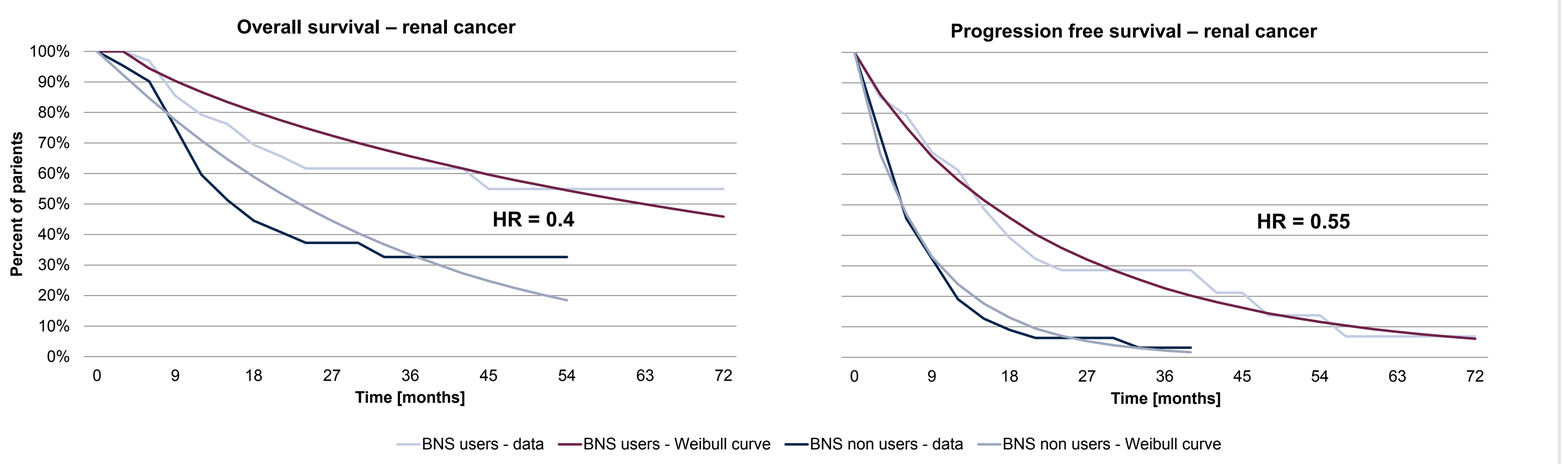


Figure 3. Overall and progression-free survival – breast cancer (Brufsky 2012 [3])

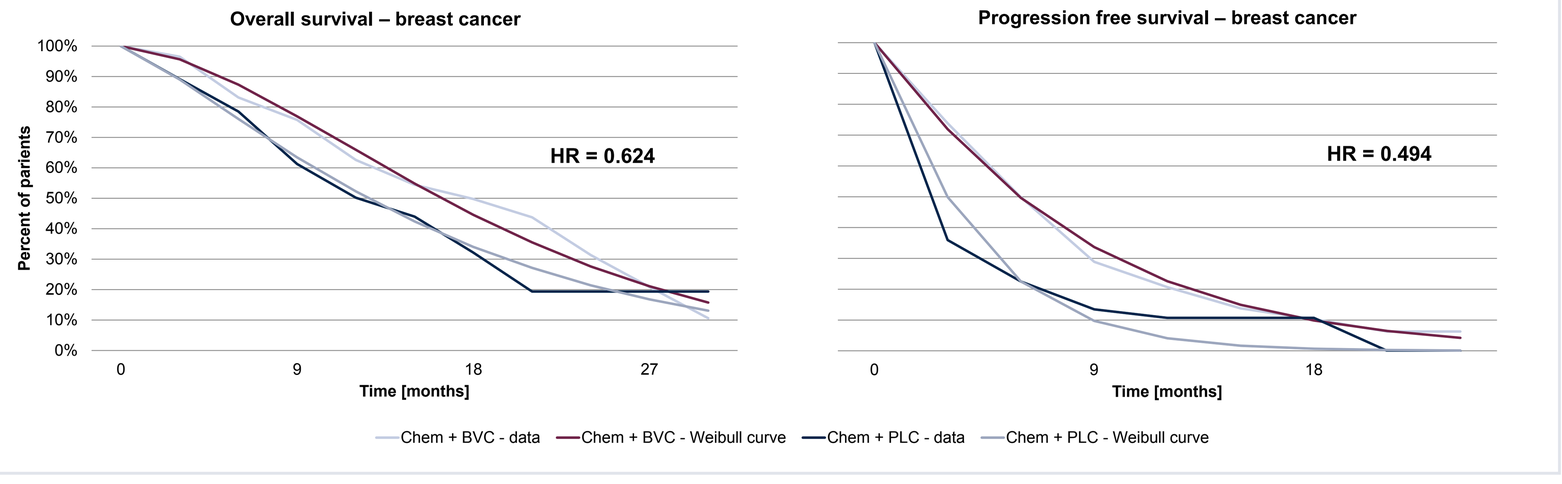


Table 2. Clinical results – breast cancer

Category		Proportional hazards assumption		
		With	Without	Difference (with vs without)
Breast cancer – differentiation of time to progression between interventions				
Progression-Free Life Years	Chem + BVC	0.64	0.68	-0.04
	Chem	0.34		-
QALY	Chem + BVC	0.72	0.73	-0.01
	Chem	0.63		-
Breast cancer – differentiation of overall survival between interventions				
Life Years	Chem + BVC	1.93	1.54	0.39
	Chem	1.33		-
QALY	Chem + BVC	0.88	0.72	0.16
	Chem	0.63		-

The results obtained from the model calculations were compiled with assumed cost differences between interventions. Cost differences between the same two interventions can vary depending on calculation option to better illustrate the influence of the proportional hazards assumption on the CEAs conclusions. Results of these calculations are presented below.

Table 3. Cost-effectiveness results – renal cell carcinoma

Comparison	Proportional hazards assumption	Assumed difference in cost	Difference in QALY	ICER [PLN/QALY]	Conclusions[a]
Renal cell carcinoma – differentiation of time to progression between interventions					
BNS users vs BNS non users	With	21 000 PLN	0.20	103 876	BNS is not cost-effective
	Without		0.39	54 118	BNS is cost-effective
Renal cell carcinoma – differentiation of overall survival between interventions					
BNS users vs BNS non users	With	110 000 PLN	1.01	108 828	BNS is not cost-effective
	Without		1.11	99 387	BNS is cost-effective

a – threshold in Poland equals 99 543 PLN

Table 4. Cost-effectiveness results – breast cancer

Comparison	Proportional hazards assumption	Assumed difference in cost	Difference in QALY	ICER [PLN/QALY]	Conclusions[a]
Breast cancer – differentiation of time to progression between interventions					
Chem + BVC vs Chem	With	10 000 PLN	0.09	110 961	Chem + BVC is not cost-effective
	Without		0.10	99 138	Chem + BVC is cost-effective
Breast cancer – differentiation of overall survival between interventions					
Chem + BVC vs Chem	With	10 000 PLN	0.24	41 301	Chem + BVC is cost-effective
	Without		0.09	115 953	Chem + BVC is not cost-effective

a – threshold in Poland equals 99 543 PLN

Conclusions

The results of our calculations indicate that, taking costs into account, proportional hazards assumption may have large impact on cost-effectiveness. With the same costs the new intervention can be cost effective or not depending on proportional hazards assumption. The impact of proportional hazards assumptions on the results of economic analysis depends on particular case. In our calculations in three cases of four the intervention was not cost-effective with proportional hazards assumption and was cost-effective otherwise. On the contrary, in the fourth case the intervention was cost effective with proportional hazards assumption and was not cost-effective otherwise.

The results of our analysis indicate that, because of its large impact on cost-effectiveness results, the proportional hazards assumption should be always checked. Furthermore, its impact on obtained results in CEAs should be estimated in sensitivity analysis.

References

1. Guyot P, Welton NJ, Ouwens MJNM, et al. Survival time outcomes in randomized, controlled trials and meta-analyses: the parallel universes of efficacy and cost-effectiveness. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011; 14(5):640–646.
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3. Brufsky A, Valero V, Tiangco B, et al. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast cancer research and treatment. 2012; 133(3):1067–1075.

Abbreviations

CEA	Cost-Effectiveness Analysis
Chem	Chemotherapy
BNS	Bisphosphonates
BVC	Bevacizumab
ICER	Incremental Cost-Effectiveness Ratio
PLC	Placebo