Abstract

Background. The main objective of this study was to evaluate the potential role of efficacy data and other information available at the time of P&R decision-making process within the definition of oncology treatment costs in Italy.

Methods. The study included all P&R dossiers submitted to AIFA between July 2015 and December 2017. It prospectively collected the data of the P&R process from dossier submission until to the IHS reimbursement decision. The cost of treatment per patient was estimated using both the list price ("gross cost") and the confidential net price ("net cost") of drug packages, and applied to the median duration of treatment. A two-sample stage Heckmann decomposition model was performed in order to evaluate the potential role of efficacy data and other information available at the time of P&R decision-making on the gross and net cost.

Results. 37 oncology drugs related to 58 therapeutic indications were analysed. The multivariate model demonstrated that the variation of PFS is the only variable predictor statistically associated with treatment cost, but this effect was observed only when confidential net prices were used (p=0.026).

Conclusions. Considering the perspective of the italian public healthcare service, the negotiation of confidential discounts or of other agreement, appears to better regulate the treatment cost in order to reflect the magnitude of clinical benefits coming from pivotal trials, than by using of transparent prices.

ORIGINAL ARTICLE

Drug prices and value of oncology drugs in Italy

Introduction

During the last decade, the price of oncology drugs has risen worldwide, becoming a critical issue for many countries in both the USA and Europe [1-4]. The global burden of cancer worsened from 2015 to 2017, with increases in incident cancer cases (17.5 and 24.5 million, respectively), cancer-related deaths (8.7 and 9.6 million, respectively), and disability-adjusted life-years (208.3 and 233.5 million, respectively) [5-6]. The availability of new and more expensive cancer therapies, combined with the increased number of eligible patients and longer time spent receiving treatment, contributed to the increase in the financial burden imposed by cancer [7].

From a payor's perspective, the economic value of new pharmaceutical products in oncology is a critical issue. Establishing the value of a drug requires an assessment of whether the additional health expected to be gained from its use exceeds the health forgone, as other treatments are displaced by its additional cost [8, 9]. In this context, the economic value of a new drug should reflect at least the magnitude of healthcare benefits [4, 7, 10]. Consequently, reimbursement decisions should be based on endpoints that may accurately predict clinically meaningful outcomes, such as survival or quality of life. This has been confirmed in both the US regulatory context of Food and Drug Administration (FDA) approvals [11] and in the European context of European Medicines Agency (EMA) approvals [12].

The following question arises: how does efficacy data (available at the time of authorisation) influence the reimbursement process? Although it may be complicated to give a definitive answer, the general idea is that there is relevant uncertainty regarding the economic value of some oncology drugs approved within the current regulatory framework.[13]. In the USA, a free-pricing market, prices of recently approved cancer drugs showed to be poorly correlated to either progression-free survival (PFS) or overall survival (OS) [14]. Therefore, US oncologists have been pushing for the establishment of a new pricing system in which Medicare can negotiate drug prices [15, 16].

In Europe, reimbursement is primarily a competence of the national drug Agencies, which act as agent representing the primary buyer (the National Health System), with different pharmaceutical regulation systems currently applied in these countries [17]. In the Italian healthcare context, regulatory approval and reimbursement decision are centrally regulated by the same institution, the Italian Medicines Agency(AIFA). This procedure consists of two steps: first, the assessment of the therapeutic value of new drugs and, subsequently, the negotiation of the price reimbursed by the Italian Healthcare Service (IHS) [18]. Moreover, Italy is one of the countries with the greatest number of managed entry agreements (MEAs) [19-21]. Both financial-based schemes (e.g., cost-sharing, budget cap, price-volume agreement, etc.) and outcome-based schemes (payment-by-result, risk sharing and success fee) have been implemented with the aim of pursuing value-based allocation of healthcare resources and controlling pharmaceutical expenditures [22-26].

The main objective of this study was to evaluate the relation between oncology treatment costs and other information available at the time of reimbursement decision in Italy. Furthermore, a secondary objective was to explore the impact of confidential agreements on drug prices, analysing oncology treatment costs using both list prices and confidential net prices reimbursed by the IHS (i.e., the price negotiated between AIFA and the pharmaceutical company).

Materials and methods

The study included all reimbursement dossiers submitted to AIFA between July 2015 and December 2017 (Supplementary Table 1), corresponding to new drugs or new therapeutic indications of authorized drugs. Different indications of the same drug were considered as different drug applications. Then, the data of the reimbursement process were prospectively collected from dossier submission until the IHS reimbursement decision (corresponding with the conclusion of AIFA negotiation). The dossiers related to oncology drugs that were not eligible for reimbursement were not included. In sum, the current study considered the first dossiers of all oncology drugs submitted over a two and a half year period, which consecutively obtained the IHS reimbursement decision during the following time.

The cost of treatment per patient to IHS was estimated using both the list ex-factory price ("gross cost") and the confidential net ex-factory price ("net cost") of drug packages. All prices exclude Value Added Tax (VAT), and they are calculated for to the median duration of treatment (median value of time-to-off-treatment curve reported in the reimbursement dossier) at the posology specified in the main pivotal clinical trial used to obtain the marketing authorisation. For a drug with multiple indications, we calculated the costs per indication on the grounds of the price negotiated when the relevant indication was approved.

The net price was defined as the list price reduced by any confidential discount and/or economic effect of Managed Entry Agreements (MEA). For performance-based agreements (namely, payment by result schemes in the Italian taxonomy), the effect was estimated as an additional discount off the drug price based on the expected performance on the grounds of pivotal studies. To estimate the additional discount of the outcome-based MEAs, the Java program "Plot Digitizer" was used to analyse the survival curves from pivotal clinical trials (Plot Digitizer 2016; https://sourceforge.net/projects/plotdigitizer/), according to a procedure already described elsewhere (see [18]). For other types of financial agreements (e.g., confidential discount, cost-sharing schemes, price-volume agreements, annual rebate, etc.), the impact was also computed as an additional discount resulting from the agreed contractual arrangement. The list price is transparent and published in the Italian Official Journal; instead, the net price resulting from nondisclosure agreements between the parties is confidential to the public. All content of reimbursement dossiers submitted to AIFA by pharmaceutical companies is sealed, except those data that were publicly available by EMA. Therefore, some details that might reveal confidential information on a specific product were not mentioned in this article and blinded to the coauthors of this work. All the confidential data considered in the analysis were managed by the coauthors employed at AIFA (MZ, MEF, AC, PR) and displayed as aggregate results.

No further costs were considered, neither those relevant from the perspective of the healthcare service (e.g., hospitalizations, drug administration or monitoring costs) nor those relevant from the perspective of the patients or society. Moreover, efficacy data in terms of median progression-free survival (PFS) and median overall survival (OS) were retrieved from the main pivotal clinical trial.

Descriptive statistics were generated for each numerical and categorical variable. Univariate analyses were performed to verify the association between the gross and net treatment costs and the categorical and continuous variables. For categorial covariates, a between-group comparison of mean values was conducted using Student's t-test. For continuous covariates, Spearman's correlation coefficients were calculated.

The distribution of cost data is typically truncated and positively skewed. This is caused by the presence of a relatively small number of treatments with higher costs (if compared with the average cost of the sample) and the absence of negative costs [27]. Due to the typically truncated and asymmetric distribution, a two-sample stage Heckmann decomposition model was performed to evaluate the relation between oncology treatment costs and other information available at the time of reimbursement decision in Italy [28, 29].

Gross and net cost were considered dependent variables. The definition of covariates reflects the same parameters that are currently considered in the reimnursement process in Italy and were categorized according to:

(i) the type of cancer (oncological/onco-haematological disease): the economic burden of onco-haematological diseases is higher than that of oncological disease, and the cost of drug treatment results in the highest burden among healthcare resources [30];

(ii) orphan designation (yes/no): although in some cases orphan designation may not capture the trade-off between volumes and prices [31], orphan drugs are usually more costly than non-orphan drugs;

(iii) number of submissions for each oncology drug (single therapeutic indication vs. multiple therapeutic indications): we assume that multiple indications could increase the total cost to IHS;

(iv) availability of comparative data on PFS or OS (single vs. double-arm data): since a single-arm pivotal trial is performed in severe or very rare clinical conditions; we expect that, in

this case, the cost should be higher than oncology drugs tested by a double-arm clinical trial;

(v) application of confidential discount (yes/no): the application of a confidential discount agreement decreases the cost to IHSand increases the gap with the list price;

(vi) presence of further MEAs (yes/no): the presence of MEAs, other than confidential discounts, further decreases the cost of treatment. MEA agreements have increased over time, particularly those for cancer diseases,[32, 33].

Other continuous variables were considered: vii) the percentage variation of PFS between the experimental and control arms; viii) the percentage variation of OS between the experimental and control arms; ix) the percentage confidential discount; and x) the effect of MEAs expressed in terms of additional discount.

The selection of the covariates for inclusion in the multivariate model was based on the results of a univariate analysis: each covariate that demonstrated a statistical association with the treatment cost variable under the $p \leq 0.1$ threshold was included in the model, while the others were excluded. The covariates of both the percentage confidential discount and the additional discount related to the MEA were analysed only by univariate analysis and were excluded a priori from the multivariate model due the mathematical relationship between the gross-to-net difference and any discounts. The covariate of the percentage variation of OS between the experimental and control arms was also excluded a priori from the multivariate model due to the limited availability of OS data and their frequent immaturity at the time of the reimbursementprocess.

Furthermore, to explore the impact of confidential agreements on drug prices, the percentage variation of the net cost after AIFA negotiation with respect to the gross cost was computed, and univariate analysis was conducted using Student's t-test.

Finally, with the aim of normalizing the variable distribution, a specific box plot analysis was conducted to exclude outlier values.

Results

From July 2015 to December 2017, 37 oncology drugs related to 58 therapeutic indications started the AIFA reimbursement procedure (Supplementary Table 1). Among these, 33 therapeutic indications (56.9%) were related to oncological diseases, while the remaining 25 (43.1%) were related to onco-haematological diseases (Table 1). Approximately half of the oncology drugs had obtained the orphan designation for the treatment of rare diseases (23 out of 25, corresponding to 92% of onco-haematological indications, and 7 out of 33, corresponding to 21% of oncological indications).

57% of the reimbursement procedures were related to oncology drugs evaluated for more than one therapeutic indication (Table 1). Moreover, in 12.1% of cases, no comparative survival data were available at the time of the reimbursement procedure. After price negotiation between AIFA and the originators, a confidential discount was agreed upon for 91.4% of oncology drugs, and further MEAs were established for 43.1% of cases (Table 1).

The univariate analysis showed that among "type of cancer" categories, the onco-haematological drugs had a higher average cost per treatment than the oncological drugs (Table 1), and this result was not affected by agreement confidentiality (mean % reduction in the net price after AIFA negotiation ±SD: -35.4%±13.7% versus -36.9%±18.8%; $p = 0.362$, respectively). The orphan status designation, the lack of comparative survival data and the absence of further MEA clauses other than confidential discounts also resulted in significantly higher average treatment costs (Table 1). At the same time, the impact agreement's confidentiality was higher when further MEA clauses were negotiated (mean % reduction in the net price after AIFA negotiation ±SD: -43.8%±14.9%) than when it was not (-30.2%±14.3%; $p < 0.001$). This result is consistent with the significant relationship found between the additional discount resulting from MEAs and the net cost (rho = -0.42 and $p = 0.036$).

In the univariate analysis, a significant relationship between the percentage variation of PFS and the treatment cost was observed, regardless of the type of cost used (gross or net), and this result was not affected by the existence of confidential agreements (gross cost: rho = 0.37 and $p = 0.016$; net cost: rho = 0.39 and $p = 0.010$).

Concerning the remaining categorical and continuous covariates, no further statistically significant effect on the average treatment cost was observed. Thus, type of cancer, orphan designation, presence of further MEAs and the percentage variation of PFS between the experimental and control arms are the covariates considered in the following analysis. With respect to the overall 58 therapeutic indications in reimbursement submissions, the analysis of percentage variation of PFS excluded therapeutic indications tested by single-arm pivotal trials (i.e., PFS in the control arm was not available; n=7) or when PFS data were not available (n=9). The multivariate analysis was finally performed using the two-stage Heckmann decomposition model after the exclusion of outliers, which were defined as drugs with percentage variation of PFS over 1.5 times the box upper threshold (Table 2). As shown in the box plot reported in Supplementary Figure 1, two outliers were identified: alectinib as a second-line treatment in adult patients with ALK-positive advanced non-small cell lung cancer previously treated with crizotinib and lenvatinib as a treatment for adult patients with progressive, locally advanced or metastatic differentiated thyroid carcinoma that is refractory to radioactive iodine. The two drugs showed large variations in PFS data (alectinib +585.7%, ALUR trial, NCT02604342 and lenvatinib +408.3%, SELECT trial, NCT01321554) compared with the mean of the sample excluding the outliers [mean (95% CI) = +81.1% (from +59.2% to +103.0%; n.=40].

The results of the two-stage Heckmann decomposition model demonstrated that the variation in PFS is the only variable significantly associated with treatment cost, but this effect was observed only when confidential net prices were used (p=0.026).

Discussion

The study findings showed a potential impact of efficacy data from pivotal clinical trials available at the time of reimbursement decision on the treatment cost of oncology drugs in Italy. The relationship between the two variables was not very strong, and it was statistically significant in both univariate and multivariate analyses only when confidential net prices (including the economic effects of MEAs) were considered. The study showed that pricing negotiation tends to be associated with lower treatment costs when lower PFS

gains were observed, particularly through greater use of MEAs in addition to simple confidential discounts. This result suggests that pricing negotiation can be considered a useful tool to achieve better value for money and to manage public expenditure. This interpretation is also sustained by a more frequent presence of further MEA clauses in addition to the confidential discount among oncology drugs associated with lower PFS gains (i.e., 62.5%, 15 out of 24 reimbursement procedures related to treatments having a % variation PFS, with respect to 37.5%, 6 out 16 procedures related to treatments under the median).

Although the influence of different clinical outcomes (OS, PFS, quality of life and safety) on the final recommendations of oncology drugs varies substantially across European countries [34], it seems that the additional therapeutic benefits (as expressed by % variation PFS) may influence the definition of drug prices in Italy. The Italian reimbursement process gives the highest premium to treatments demonstrating additional benefits in terms of OS (i.e. greater efficacy than alternative therapeutic options in clinically relevant outcomes, ideally curing the disease or altering its natural history) [35]. Our data did not show a significant impact of the outcome of OS on reimbursed prices of recently approved oncology drugs. Decision-makers usually need additional information that is rarely available before the reimbursement decision such as relative efficacy data versus frequently used drugs in clinical practice, as well as long-term efficacy data.

In the literature, the relationship between incremental efficacy data and the related drug costs has been explored in several other studies, without observing a significant correlation [14, 36, 37]. When list prices were considered, our study found a weak correlation between the two variables only in the univariate analysis, while a significant relationship in both univariate and multivariate analyses was observed using net prices. However, in comparison with previous studies [14, 37], some methodological differences may explain different conclusions. In particular, the main differences regarded the calculation of treatment costs and the use of list prices reduced only by the effect of confidential discounts. Instead, our results appear to be in line with those conducted on drugs that underwent German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) appraisal, reporting a positive association between the negotiated annual

treatment cost of new medicines and the extent/certainty of benefits (no, 'nonquantifiable', 'minor', 'considerable', and 'major' additional benefit) [38].

Some limitations of this study should be highlighted. First, other factors that may play a role in the reimbursement process were not considered. On this topic, AIFA published a guideline that identified important parameters in the reimbursement process: (i) the unmet medical need; (ii) the other health benefits over existing alternative therapies (not only in terms of clinical efficacy); (iii) the relative price compared with alternative drugs already available in the market; and (iv) the cost savings in terms of other healthcare resources [39, 40]. Future analysis should also explore the impact of these parameters as independent variables in our model.

Second, the nondisclosure covenant of negotiated drug prices has been the subject of a sustained debate for a long time- In this regard, it has been argued that the use of MEAs may undermine the principle of accountability, since the cost of innovative treatments is financed by public financial resources. [33]. A recent WHA resolution called for greater collaboration across countries to facilitate the sharing of information on the net prices of healthcare products [26]. However, there is no general consensus on the real advantages of price transparency ,because the spectrum of transparency's implications is very wide, affecting the public expenditure of every single country up to the dynamic of the global pharmaceutical market [41]. For instance, it can be argued that efforts to increase price transparency are likely to result in a lower degree of price differentiation and, consequently, a limited access to innovative pharmaceuticals [42]. Nevertheless, MEAs can be considered an additional negotiation option to grant a positive reimbursement status, and this study provides empirical evidence on the extent to which confidential agreements reduce drug costs from a public healthcare perspective. However, divergent opinions exist on this topic, some suggesting that originators may inflate the financial gains of MEAs by setting higher list prices [43], while other analyses conducted in Germany on oncology drugs did not find evidence that manufacturers set higher launch prices [44]. Gamba et al. [43], using a theoretical model applied to a sample of 156 medicines in six countries, showed that the presence of an MEA leads to a 5.9% higher list price than when it is absent. However, the current study also provides data that if this effect was present, it would

be largely balanced by the economic effect of MEAs (expressed in terms of additional discount), which account for a 28.1% mean reduction in the cost of treatment (95% CI: 21.2% to 35.0%, see Table 1). Although the aim of the study was not to verify the actual efficacy of MEAs (other than the confidential discount), the oncology drugs associated with MEAs displayed a significantly lower average net cost of treatment, and the additional discount expressing the economic effect of MEAs was significantly related to the net cost of treatment. However, when the presence of MEAs was considered in the multivariate analysis together with a parameter expressing the added therapeutic benefit of the oncology drug (i.e., the % variation of PFS), only the effect of this last covariate remained statistically significant. Regardless of financial gains in terms of reducing the cost of treatment, MEAs are useful when payers have to manage uncertainty about effectiveness, safety and appropriate use in real-world practice [33]. This concept has found wide application in Italy, which has adopted a registry-based application of MEAs at the patient level since 2005 [24].

Finally, the model is based on data on median progression-free survival or overall survival retrieved from pivotal clinical trials. These outcomes reflect the patient selection studied to obtain the authorisation of therapeutic indication (i.e., efficacy data). Instead, when the reimbursement process addresses the limitation of reimbursement according to the features of patient subgroups in pivotal trials, it always considers patient subgroups with better outcomes (i.e., higher median PFS) than that in the overall trial population. Thus, although the PFS data may be biased, our analysis should have yielded conservative results, as it may underestimate the actual improvement in PFS among patients eligible for reimbursement in real-world clinical practice.

In Italy, the difference between the gross and net cost of new drugs occurs due to the negotiation process, which is currently implemented in several other European countries [17] and it has been considered in the context of healthcare in the US [7, 23, 45]. Our study showed that the negotiation process was able to achieve a mean reduction of 33% in the cost of treatment with oncology drugs. This finding is in line with that recently reported on a panel of 57 anticancer drugs in Germany, where the introduction of price negotiations led to a 24.5% decrease in negotiated prices relative to launch prices [44].

Conclusion

In conclusion, this study findings provide further support to the literature on the usefulness of negotiation of confidential discounts or other MEAs to ensure that treatment costs of innovative oncology drugs better reflect the magnitude of clinical benefits and, to some extent, the drug value for patients and society as a whole. Considering the perspective of a developed country having a public healthcare service with a central reimbursement negotiation is determined a relevant reduction in the treatment cost sustained by public payers. This is a useful approach to guarantee both the affordability of innovative oncology drugs and to contain public expenditures on healthcare. Furthermore, the negotiation of confidential discounts and agreement clauses in MEAs appeared to reward oncology drugs displaying an added therapeutic benefit.

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Tables and Figure Legends

Table 1. Univariate analysis of the association between the treatment costs of oncology drugs in Italy (computed using both list price and confidential net price) and the categorical and continuous covariates.

	N of submissions (%)	Average gross treatment cost (€)	*p*-value	Average net treatment cost (€)	*p*-value
Categorical variables					
Total REIMBURSEMENT submissions	58 (100.0)	84,202	-	56,494	-
Type of cancer					
Oncological	33 (56.9)	61,727		39,195	
Onco-haematological	25 (43.1)	113,869	0.002	79,329	0.004
Orphan designation					
Yes	30 (51.7)	109,404		76,974	
No	28 (48.3)	57,200	0.002	34,551	0.002
Number of submissions for the same oncology drug					
Single indication	25 (43.1)	84,085		57,736	
Multiple indications	33 (56.9)	84,291	0.991	55,553	0.880
Availability of comparative data (PFS or OS)					
Double arms data	51 (87.9)	73,548		46,445	
Single arm data	7 (12.1)	161,828	<0.001	129,713	<0.001
Confidential discount					
Yes	53 (91.4)	82,335		53,316	
No	5 (8.6)	103,992	0.492	90,183	0.145
Presence of MEAs					
Yes	25 (43.1)	62,225		35,129	
No	33 (56.9)	100,825	0.028	72,680	0.007
Continuous variables	**Mean (95% CI)**	**Spearman's rho**	***p*-value**	**Spearman's rho**	***p*-value**
Variation of PFS (n=42)	100.9% (65.5% to 136.3%)	0.37	0.016	0.39	0.010
Variation of OS (n=21)	48.6% (30.4% to 66.8%)	-0.20	0.378	-0.14	0.533
Confidential discount (n.=53)	26.4% (22.6% to 30.2%)	0.22	0.106	0.09	0.540
MEA discount (n=25)	28.1% (21.2% to 35.0%)	-0.33	0.112	-0.42	0.036

Table 2. Results of two-stage Heckmann decomposition models applied to treatment costs of oncology drug, computed using as dependent variable both the gross treatment cost and the confidential net treatment cost after AIFA negotiation.

Gross treatment cost	**Coefficient**	**SE**	**z value**	***p*-value**
Intercept 1	54,510.00	22,690.00	2.40	0.016
Intercept 2	10.60	0.12	89.33	<0.001
Type of cancer				
Oncological	Ref.			
Onco-haematological	-11,790.00	21,450.00	-0.55	0.582
Orphan designation				
No	Ref.			
Yes	4,259.00	21,500.00	0.20	0.843
% Variation of PFS	14,460.00	9,621.00	1.50	0.133
Net treatment cost	**Coefficient**	**SE**	**z value**	***p*-value**
Intercept 1	31,648.45	12,200.57	2.59	0.009
Intercept 2	9.96	0.12	84.85	0.001
Type of cancer				
Oncological	Ref.			
Onco-haematological	-4,731.15	11,417.43	-0.41	0.679
Orphan designation				
No	Ref.			
Yes	846.60	11,373.84	0.07	0.941
Presence of MEAs				
No	Ref.			
Yes	-5,585.72	7,025.38	-0.80	0.427
% Variation of PFS	11,523.90	5,177.04	2.23	0.026

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