Time to market and patient access to new oncology products in Italy: a multistep pathway from European context to regional health care providers

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Aim: The main purpose of this study was to identify each sequential phase followed by an oncology product, from European assessment until to patient access in each Italian region (IR).

Methods: A panel of oncology products approved by the European Medicines Agency (EMA) in the period 2006–2008 was considered. The explored sequential phases included the times to market for: the EMA; pharmaceutical companies; the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA); and IRs as final providers of health care. The IR’s time to market was also analyzed by a Cox regression model.

Results: The overall mean time required before patients access was 2.3 years. EMA accounted for the greater proportion of time (31.8%), followed by AIFA (28.2%). However, the duration for both pharmaceutical companies and IRs was associated with the highest variability. An oncology product authorized with a risk-sharing agreement showed an early access in the IRs. On the contrary, the introduction in IRs having a compulsory formulary was delayed. Both a high forecast of economic impact and a high oncology product price can also delay the patient access.

Conclusion: The process before patient access to an oncology product is time and cost consuming. This study identifies the main predictors that affect the missing overlap between market and patient access in Italy.

Key words: accessibility, regulatory, reimbursability

introduction

The impact of oncology medicines is USA$ 48 billion worldwide, and this is the first therapeutic class with highest sales and a relevant growth rate of 11.3% in 2008 [1]. The current scenario has been developing since 2005, when the research and development (R&D) in the area of oncological diseases led to the introduction of new target therapies [2].

The Italian pharmaceutical market is the fifth in the worldwide ranking [3], with an overall expenditure of >€24 billion [4]. The economic impact of oncology medicines corresponds to ~€1.3 billion. Despite the relevance of pharmaceutical expenditure, the amount of investments for R&D in Italy is at the fifth place in the European ranking with a value which is about three-fold lower than the fourth country (Switzerland with €3 billion [3]).

Furthermore, the Italian context is characterized by a rigorous regulation of the medicine introduction [5]. In particular, among European countries, in Italy there is a central legislative power (which defines both reimbursability and price of drugs for the Italian National Health Service—NHS) and a region’s responsibility that must organize locally medicine’s supply for health care.

A recent international survey on oncology medicines showed that Italy has the longest average time between first worldwide launch and the access to patient, among European countries with solid pharmaceutical sales statistics [6]. This survey also showed inequalities in the new oncology medicines uptake mainly dependent on the specific attractiveness of domestic market (both in terms of value and accessibility).

For all these reasons, the Italian context could represent a paradigmatic case study for the accessibility to oncology medicines. The main purpose of this study was to quantify the time between the completion of R&D and the patients access for each Italian region (IR), considering a panel of oncology products approved by the European Medicines Agency (EMA) from 2006 to 2008.

According to the definition of the Organisation For Economic Co-Operation and Development [7], R&D represents a set of activities ranging from basic research to experimental development. Thus, the date that the dossier is submitted to EMA for a new oncology product assessment could be considered almost as a final step of R&D, and a first step before patients access.
Moreover, in order to explore the influence of decision-making process on the health care organization, an additional aim of the current study was to identify relevant predictors of patients access to this important therapeutic class in every IR.

**Methods**

The market and patients access to new oncology medicines were analyzed considering the time span along the multistep pathway from the European context to regional health care providers.

The time elapsed between R&D completion and patients access to a new oncology medicine has been defined as the difference between the date of the first purchase of an oncology product by at least one health care public structure in at least one IR and the validation date of EMA’s centralized procedure for the same product.

Some methodological considerations should be posed on the interval’s limits. Although the date of the first medical prescription should have been considered as the real index date of a patient access, the date of first purchase has been considered as a ‘proxy’ in the current study. Indeed, the purchase indicates the availability of drug within the public structure exclusively and may occur few days before its actual use.

Despite the application date for a centralized procedure to EMA being a good reference of R&D completion, the experimental development of a new product could go over this date (e.g. delayed conclusion of some registration clinical trials, supplementary applications to regulatory authorities for the extension of therapeutic indications).

**Panel of the oncology products**

The evaluated panel of oncology products has been defined according to the chronological criterion of EMA’s centralized licensing procedure. In particular, all licensed medicines with therapeutic indications for the treatment or prevention of oncological diseases, and also those indicated for the treatment or prevention of side-effects of cancer therapy have been selected in the period between 2006 and 2008 (Table 1).

**Data source**

Data were obtained from the European Public Assessment Report by EMA (http://www.EMA.europa.eu/htms/human/epar/eparintro.htm) and from the official administrative acts of marketing authorization published on both the Italian and European Official Journal. In addition, the application date of price and reimbursement dossiers submitted to the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) has been identified; this date refers to the first application, excluding all possible further dossiers of the same product for any extension of therapeutic indications, or other procedures.

Monthly data for the purchase of oncology products by every region has been extracted from ‘Traceability database’ of the Italian Ministry of Health [8]. This database includes a monthly track of every handling of medical products toward every structure of the Italian NHS (established with Ministry Decree, 15 July 2004). Thus, in the definition of purchase date, the start of patient access has been attributed to the first day of the first handling month. Data were drawn from the traceability database in the time span between January 2006 and March 2009 (last available data).

**Sequential phases of the multistep pathway**

The considered sequential phases of the multistep pathway from European assessment until access in Italy are the following:

1. **EMA time: interval computed as the difference between the date of EMA-positive opinion and the validation date of centralized procedure.**

2. **Pharmaceutical company time: interval computed as the difference between the application date of the price and reimbursement dossier submitted to AIFA and the date of EMA-positive opinion.**

3. **AIFA time: AIFA is the national agency responsible for market authorization of medicines in Italy. Every medicine receiving EMA’s authorization can be marketed in Italy only after AIFA releases reimbursability and negotiated price for the Italian NHS.**

4. **Regional time: new federal rules have been introduced in Italy, assigning to the 21 IR the responsibility of the health care organization, including pharmaceutical assistance and related charges.**

The overall number of ‘clock stop’ days during the assessment procedure (generally depending on additional request of technical documentation from EMA experts to pharmaceutical company) has been subtracted from EMA time.

The overall number of clock stop days accumulated during the previous EMA assessment procedure. Obviously, this time cannot be calculated when the pharmaceutical company decides not to introduce the oncology product into the Italian market.

**Table 1. List of oncology products approved by EMA between 2006 and 2008**

<table>
<thead>
<tr>
<th>Product</th>
<th>Active substance</th>
<th>Date of EMA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVOLTRA</td>
<td>Clofarabine</td>
<td>29 May 2006</td>
</tr>
<tr>
<td>SUTENT</td>
<td>Sunitinib</td>
<td>19 July 2006</td>
</tr>
<tr>
<td>NEXAVAR</td>
<td>Sorafenib</td>
<td>19 July 2006</td>
</tr>
<tr>
<td>SAVENE</td>
<td>Dexrazoxane</td>
<td>28 July 2006</td>
</tr>
<tr>
<td>GARDASIL</td>
<td>Human papillomavirus vaccine</td>
<td>20 September 2006</td>
</tr>
<tr>
<td>SPRYCE</td>
<td>Dasatinib</td>
<td>20 November 2006</td>
</tr>
<tr>
<td>ADVAGRAF</td>
<td>Tacrolimus</td>
<td>23 April 2007</td>
</tr>
<tr>
<td>REVLIMID</td>
<td>Lenalidomide</td>
<td>14 June 2007</td>
</tr>
<tr>
<td>ATRIANCE</td>
<td>Neralabine</td>
<td>22 August 2007</td>
</tr>
<tr>
<td>YONDELIS</td>
<td>Trabectedin</td>
<td>17 September 2007</td>
</tr>
<tr>
<td>CERVARIX</td>
<td>Human papillomavirus vaccine</td>
<td>20 September 2007</td>
</tr>
<tr>
<td>TORISEL</td>
<td>Tensirolimus</td>
<td>19 November 2007</td>
</tr>
<tr>
<td>TASIGNA</td>
<td>Nilotinib</td>
<td>19 November 2007</td>
</tr>
<tr>
<td>VECTIBIX</td>
<td>Panitumumab</td>
<td>03 December 2007</td>
</tr>
<tr>
<td>THALIDOMIDE</td>
<td>Thalidomide</td>
<td>16 April 2008</td>
</tr>
<tr>
<td>PHARMION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYVERB</td>
<td>Lapatinib</td>
<td>10 June 2008</td>
</tr>
<tr>
<td>CEPLINE</td>
<td>Histamine dihydrochloride</td>
<td>07 October 2008</td>
</tr>
<tr>
<td>VIDAZA</td>
<td>Azacitidine</td>
<td>17 December 2008</td>
</tr>
<tr>
<td>MEFACT</td>
<td>Milamertine</td>
<td>06 January 2009</td>
</tr>
<tr>
<td>FIRMAGON</td>
<td>Degarelix</td>
<td>16 January 2009</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency.
between the date of the first purchase of oncology product by at least one public health care structure in every IR and AIFA market authorization. Furthermore, to identify if patients access was stable in time, the purchase date has been also defined according to the handling month in which the volume corresponded to at least to 20th percentile of the overall volume of the given product.

**statistical procedures**

In order to measure the magnitude of interproducts variability of each sequential phase, a variation coefficient was computed as a percentage ratio between standard deviation of the number of days calculated for each oncology product and the corresponding mean value.

To identify the potential predictors of time to patient access in every IR, a Cox regression model was designed. Thus, the considered dataset was composed by the time to patient access between AIFA market authorization and the date of the first purchase of every product by at least one public structure in every IR, or until 31 March 2009 for the censored cases. The regression model considered the following predictors:

- oncology product labeled or not labeled as an orphan drug;
- oncology product introduced in a region with or without a compulsory regional formulation;
- oncology product authorized with or without a risk-sharing agreement;
- forecast of the economic impact for the NHS in the first 3 years of commercialization;
- ex-manufacturer price after AIFA negotiation;
- forecast of the annual cost per patient at negotiated price.

Economic predictors data were obtained from the acts of marketing authorization published on the Italian Official Journal, and from the price and reimbursement dossier submitted to AIFA. With the aim of adjusting for the typical skewness of economic data [9], these predictors were log transformed.

To compare the times to patients access at regional level, a Kaplan–Meier analysis (with Breslow test) was also carried out on the basis of statistically significant categorical predictors identified by the Cox regression model.

**results**

In the time span between 2006 and 2008, EMA authorized 20 oncology products; of these, 75% were also labeled as orphan drugs for the treatment of rare diseases (Table 2). At the moment, pharmaceutical companies have requested the introduction of 90% of EMA-authorized products into the Italian market (18 out of 20). AIFA completed the national assessment of 88.9% of those products (i.e. 16 out of 18 oncology products). The remaining two products are currently under AIFA evaluation.

Table 3 shows the results of market and patients access to oncology products in Italy. The mean time of EMA evaluation of quality, efficacy, and safety for the considered panel of oncology products was 278 days, while AIFA required a marginally lower mean time of 261 days. Along the multistep pathway toward patient access, the sequential phases with the lowest variability were those of regulatory authorities (i.e. 19.2% and 39.0% for EMA and AIFA, respectively), while a relevant variability affected both pharmaceutical company time (151 mean days with a coefficient variation of 87.0%) and Regions times (160 mean days with a coefficient variation of 89.5%).

Among the 20 oncology products authorized by EMA, 14 products have achieved patients access in Italy (Table 3). The six remaining products are missing for the following reasons:

- the pharmaceutical companies have not yet submitted any price and reimbursement dossier to AIFA (n = 2);
- AIFA evaluation is not yet completed (n = 2);
- AIFA authorization occurred in March 2009, therefore they cannot still be considered (n = 2).

Patients access in Italy for the panel of oncology products required an overall mean time of 857 days (2.3 years), with a min–max range of 1.4–3.9 years. The longest phase is represented by EMA assessment, absorbing the 31.8% of the overall time, followed by AIFA phase, absorbing the 28.2% of time. The time closely dependent on Italian context (regions time plus AIFA time) represents <50% of the total time (i.e. 46.9% or a mean of 402 days).

The incidence of pharmaceutical company time was of 18.5%, corresponding to a mean time of 159 days. This phase displayed the highest variability (90%), considering a time to dossier submission to AIFA ranging from 42 days to 1.2 years after the EMA-positive opinion.

The percentage of patient access by IRs among the 14 oncology products is shown in Table 4. Patients access was not simultaneously achieved for all oncology products in every IR, with percentage of access ranging between 50% and 85.7%. This scenario becomes worse if a more conservative approach in the definition of access date is considered. In fact, in some regions, a stable patients access could also be achieved for <50% of AIFA-authorized products.

**Table 2.** Frequency by year for oncology products authorized by both EMA and AIFA

<table>
<thead>
<tr>
<th>Year of EMA authorization</th>
<th>Europe (EMA)</th>
<th>Italy (AIFA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of products</td>
<td>No. of products for rare diseases (% on no. of products per year)</td>
</tr>
<tr>
<td>2006</td>
<td>7</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>2007</td>
<td>7</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>2008</td>
<td>6</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>15 (75.0)</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; AIFA, Italian Medicines Agency (Agenzia Italiana del Farmaco).
The selective analysis of antitumor agents alone does not substantially change the picture of market and patients access showed in the Table 3; however, a small shortening in the overall mean time of 38 days was observed (i.e. passing from 857 to 819 days). This result is characterized by a small average increase of both EMA and AIFA time (now absorbing 34.2% and 31.4% of the overall time, respectively), which is then more than offset by a decrease of both pharmaceutical company and regional time (now absorbing 17.1% and 14.4% of the overall time, respectively).

Table 5 shows the potential predictors of the time to regional patient access in Italy, identified by the Cox regression model. The regression analyzed a dataset composed by 14 oncology products in each of the 21 regions (i.e. 294 overall cases). Censored cases were 78 (26.5% of total) and concerned oncology products authorized by AIFA 1 year before. Several variables significantly predicted the time to regional patients access. The strongest predictor was that considering the oncology products with a defined risk-sharing agreement in the context of AIFA authorization. On the contrary, a significant prolongation of the time to access was present for those products introduced in regions with a compulsory formulary, or with a high forecast of the economic impact during the first 3 years of commercialization, or a high product price.

Finally, to compare the mean time to access according to either the introduction in region with or without a compulsory regional formulary (Figure 1A) or authorization with or without a risk-sharing agreement (Figure 1B), two Kaplan–Meier analyses were carried out. The mean prolongation of the time to access in regions with a compulsory formulary was 45 days [i.e. a median of 227.6 days standard error of mean (SEM) = 18.3] for the access in regions 'with' a compulsory formulary versus a median of 182.5 days (SEM = 22.3) for the access in Regions without a compulsory formulary; $P = 0.0377$, Figure 1A], while the authorization with a risk-sharing agreement was associated with a rapid patient access, characterized by a mean shortening of 256 days [i.e. a median of 83.7 days (SEM = 14.6) for the access of products authorized with a risk-sharing agreement versus a median of 342.7 days (SEM = 20.8) for the access of products authorized without a risk-sharing agreement; $P < 0.001$, Figure 1B].

discussion

The current analysis showed that the drug assessment before patients access, even in the case of important drugs such as those for the treatment of oncological diseases, is a complex process, time and cost consuming. On average, the overall interval between R&D completion of an oncology product and the patient access is ~2.3 years (857 days).

The greater proportion of time is required by EMA for the assessment of efficacy, safety, and quality of oncology products, before the European centralized authorization. On average,
EMA has taken ~9 months to complete an assessment, although the actual mean time needed to obtain the centralized authorization (i.e. that included also clock stops during the EMA procedure) corresponded to 441 days (14.5 months). EMA centralized authorization is not immediately followed by the access in all European markets; in fact, national agencies subsequently regulate the final access in every domestic market.

In Italy, the submission of price and reimbursement dossier to AIFA is the first step before market and patient access to every medicine for Italian people [10]. Obviously, the lag time between EMA authorization and market access in Italy depends on pharmaceutical companies and could be variable according to the market access strategies of pharmaceutical companies in several European countries or their efficiency in the management of regulatory workload.

The current study has shown that this lag time is on average 5 months. This delay could explain, at least in part, the previously registered difference between patient access in Italy to oncology drugs authorized before 2006, and other European countries [11]. Kos et al. [11] showed that Italy and Slovenia are the last European countries where patients access is achieved, with a maximum delay of 1 year compared with the UK, Germany, or Switzerland. Certainly, the decision of a pharmaceutical company to delay or not launch a product in a specific country is influenced by potential global profits. On this note, several factors seem to affect the decision [12], such as external price benchmarking (i.e. the influence on pricing in other countries due to the settled price in a specific country), parallel trade, and local market size. In the context of AIFA price negotiation, an external price benchmarking with France or Spain may be carried out [13]. Currently, Italy is the European country with the best performance on drug price negotiation, having the lowest mean level of ex-manufacturer drug prices [14]. However, adopting an opposite perspective, pharmaceutical companies may be induced to delay the introduction of a new medicine in Italy, in order to avoid the use of Italy as external price benchmark for other countries.

After dossier submission to AIFA, on average 8 months are required to decide on reimbursement and to set the Italian NHS price for the considered panel of oncology products. Although the National Institute for Health and Clinical Excellence (NICE) does not set the price of medicines, a possible comparison with AIFA decision-making performance may be done. Recently, in order to deliver faster guidance to the UK NHS, NICE introduced a new appraisals process named as single-technology appraisals. A recent survey showed that, in the cases of cancer-related single-technology appraisals, the average time corresponded to 12.8 months [15].

To our knowledge, this is the first analysis that explored the impact of regional factors on the time to patient access. On this issue, the main result is the evidence that market access does not correspond with patient access.

Actually not all the oncology products authorized by AIFA are subsequently released in every IR, and the mean delay from patient access was 5.3 months. The statistically significant relationship between economic predictors and time to regional access is consistent with the problem of sustainability of pharmaceutical expenditure. This issue is especially relevant in the case of cancer therapies, where costs of care have generated some concerns [16]. Furthermore, it should be noted that in Italy, strict budget constraints to both national and regional pharmaceutical expenditure are in force [10].

A further barrier to patients access in Italy is represented by the dominant role gained by regional formularies over the national formulary. In general, there is no doubt that every formulary can be a tool for efficient resources allocation and for appropriate prescriptions. However, the introduction of innovative and high-priced products may be hampered by a formulary, if market access is not linked with financing schemes taking into account the current and incremental resources actually available in every local health budget. In fact, this study showed that oncology products receiving a market authorization combined with a risk-sharing agreement had a very fast patient access.

All purchasing decisions are tied to some degree of uncertainty on the impact of new technologies in the real-world practice, and the consequences of inefficient choices may be relevant [17]. In this way, in some European countries, innovative approaches to increase patients access has been
adopted, such as the conditional reimbursement based on risk-sharing agreements [18]. Typically, these arrangements are based on a ‘guaranteed’ outcome (clinical or financial or economic) resulting from the treatment. Italy is one of the first countries where risk-sharing agreements for oncology products have been introduced (i.e. from 2006), and the results of monitoring registry are publicly available [19].

Some limitations in the interpretation of study results should be considered. Actually, there were specific reasons for delays in every oncology product along the multistep pathway, although their analysis goes beyond the scope of the current study. However, some speculation could be done according to the median split of EMA time for every oncology product. In fact, the oncology products with a longer EMA time also showed a longer AIFA plus regions time [group with EMA time ≥261 days having an AIFA plus regions median time of 395 days (interquartile range 387–432), versus group with EMA time <261 days having an AIFA plus regions median time of 276 days (interquartile range 250–311); P = 0.019, Mann–Whitney test]. In other words, for those products for which soundness and relevance of clinical evidences are probably clearer, the multistep pathway is followed more quickly from the beginning.

Moreover, the current study cannot support a causal relationship between the observed IR differences (in terms of both percentage of available oncology products and time to patient access) and coherent differences in the overall health outcomes. Although there are no doubts that the overcoming of barriers to an equitable access to health care produces better outcomes [20, 21], a between-regions transfer of patients to

Figure 1. Kaplan–Meier analyses of time to regional patient access according to either the introduction in Region with or without a compulsory regional formulary (A) or authorization with or without a risk-sharing agreement (B).
obtain quality care is possible, and this may compensate for inequalities in patient access among IR.

In conclusion, this analysis provides data on drug accessibility referred to the Italian health care context. The overall picture is a complex puzzle composed by opposite perspectives (public health and private profits), by different assessment criteria (EMA and domestic criteria), by different market access strategies in European countries (depending on the comparison of domestic rules and hurdles), by different market sizes, and by different regional perspectives (depending on their budget constraints and their health care organization and attractiveness), which influence the market and patient access also to priority medicines such as those authorized by EMA’s centralized procedure having therapeutic indications in oncological diseases.

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disclosure
None of the authors declare conflicts of interest.

references