MINI-REVIEW

A Uniform Procedure for Reimbursing the Off-Label Use of Antineoplastic Drugs According to the Value-for-Money Approach

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Summary

National healthcare systems as well as local institutions generally reimburse numerous off-label uses of anticancer drugs, but an explicit framework for managing these payments is still lacking. As in the case of on-label uses, an optimal management of off-label uses should be aimed at a direct proportionality between cost and clinical benefit. Within this framework, assessing the incremental cost/effectiveness ratio becomes mandatory, and measuring the magnitude of the clinical benefit (e.g., gain in overall survival or progression-free survival) is essential.

This paper discusses how the standard principles of cost-effectiveness and value-for-money can be applied to manage the reimbursement of off-label treatments in oncology. It also describes a detailed operational scheme to appropriately implement this aim. Two separate approaches are considered: a) a trial-based approach, which is designed for situations where enough information is available from clinical studies about the expected effectiveness of the off-label treatment; b) an individualized payment-by-results approach, which is designed for situations in which adequate information on effectiveness is lacking; this latter approach requires that each patient receiving off-label treatment is followed-up to determine individual outcomes and tailor the extent of payment to individual results.

Some examples of application of both approaches are presented in detail, which have been extracted from a list of 184 off-label indications approved in 2010 by the Region of Tuscany in Italy. These examples support the feasibility of the two methods proposed.

In conclusion, the scheme described in this paper represents an operational solution to an unsettled problem in the area of oncology drugs.

Key words: Off-label pricing, anticancer drug pricing.

INTRODUCTION

The prices of innovative anticancer agents are very similar in European countries, despite the differences in the decision processes adopted by different countries for price determination. Some countries employ value-based procedures, while others do not.1-3 The group of countries that do not adopt the value-for-money approach tends to fix the price of drugs at the same price levels adopted by the group of countries that use value-for-money, probably because the latter acts as a reference point for the former.

Similar to on-label uses, the price of off-label uses should reflect the clinical benefit, i.e., a value-based price. However, employing the on-label price to pay for off-label uses is inappropriate because there is no direct relationship between the on-label price of a drug and the clinical benefit resulting from its off-label use. In addition, the presence of payment by result mechanisms for numerous on-label uses makes this problem even more pronounced. In these cases, on-label uses are paid at prices reduced by the payback process, whereas off-label uses of the same drug are paid at full price.

Using the value-based approach to price on-label indications is likely to produce robust decisions because in these cases the clinical benefit has reliably been determined, e.g., through controlled clinical trials. On the other hand, using this methodology for off-label indications tends to increase the risk of inappropriate decisions because the effectiveness data for off-label uses are generally less sound than the data for on-label uses. Hence, off-label uses need more flexible schemes depending on the amount of effectiveness data available.

In this context, our paper focuses on the methods that can be used for applying the value-for-money approach 4-6 to the off-label use of oncology drugs, particularly the most expensive ones.

DETERMINING THE VALUE-BASED PRICE FOR OFF-LABEL TREATMENT: TRIAL-BASED VERSUS INDIVIDUALIZED PAYMENT-BY-RESULTS APPROACH

According to the schemes presented in this paper, when the value-for-money approach is applied to the off-label use of oncology drugs two different approaches can be used for tailoring the price to the magnitude of the clinical benefit: a trial-based approach and an individualized payment by results approach. Both of these approaches are evidence-based.

In the trial-based approach, the magnitude of the effectiveness of the off-label drug is assessed from the results of the original clinical trial, while in the individual-based approach the clinical benefit is measured from individual cases. In both cases, the value-based price is determined by applying the cost-effectiveness ratio, wherein the drug price is the parameter to be calculated.

Trial-based approach

In this case the value-based price is calculated using the following equation:

\[ \text{Suggested Payment}_{A} = C_{A} \times \left( S_{1} - S_{O} \right) \]

where Treatment A is the potentially innovative off-label therapeutic modality. Treatment B is the standard therapeutic modality.
ility for the same clinical indication. SUGGESTED PRICE, [EUR/patient] is the maximum price that can be recognized to Treatment A for each patient treated off label. C, [EUR/patient] is the actual cost for Treatment B. S, [months/patient] is the survival expected, on the basis of literature information, for each patient receiving Treatment A. S, [months/patient] is the survival expected, on the same basis, for each patient receiving Treatment B. The constant of 5,000 EUR per month gained (i.e. 60,000 EUR per life year gained) is the cost-effectiveness threshold adopted in our analysis.2,3,11

The approach implemented in Equation 1 assumes that the payer accepts that the effectiveness observed in the trial will be reproduced in each patient treated in the "real world." The benefit in the "real world" is not however measured in individual patients who are not therefore subjected to any prospective measurement of outcomes. Hence, in the absence of these outcome measurements, all patients are handled at the same level of payment, irrespective of the benefit generated by the individual cases. In summary, this model of payment has no inter-patient variability, but is exclusively based on average population estimates derived from the results of the clinical trials.

One disadvantage of this approach is that the risk that the real effectiveness is less than that expected from the clinical trials is entirely taken by the payer, while the manufacturer does not participate at all in this risk. Another disadvantage of this approach is that there would be as many different off-label prices as the number of different off-label uses approved by reimbursement. Clearly, this can be impractical from an operational point of view.

**For the same drug - Individualized payment-by-results approach**

In this case, each patient given the off-label treatment must be included in a prospective follow-up programme and the risk that the real clinical benefit is less than that expected from the trials is shared between the payer and the manufacturer. Accordingly, the equation implementing this approach is as follows:

\[
\text{PAYBACK} = (\text{REAL EXPENDITURE}) - (C_x + 5000 \times (S_x - S_y))
\]

where S, [months/patient] is the survival observed in the patient under examination receiving Treatment A. S, < S, the difference of S, S, is set to zero to avoid the paradoxical result in which the manufacturer does not make any payback and is in addition entitled to receive an extra payment that exceeds the real expenditure already incurred by the payer for the individual patient.

From an operational standpoint, this payback procedure is based on the assumption that, firstly, all treatments are fully paid using the on-label price of the drug. Then, individual outcomes of the off-label treatment are assessed, and allows determination of the economic equivalence (Authors, do you mean "equivalent"???/Equivalent countervalue is not clear) of the off-label treatment. Finally, a patient-specific balance is made in which the manufacturer is recognized only two economic quantities: a) the economic countervalue of the clinical benefit realized by the individual patient, and b) the hypothetical cost of Treatment B if B had been given to the patient. In other words, the manufacturer is asked to pay back the entire expenditure for the off-label treatment detracted by these two quantities. In the event that these two quantities exceed the real expenditure, no payback is requested, but of course the payer is not requested to incur any additional payment related to the occurrence of a benefit greater than expected.

**Operational procedure**

The operational procedure for both the trial-based and the individualized payment-by-results approach is reported in detail by describing an example represented by the off-label use of bevacizumab in ovarian cancer.

The preliminary results of a few clinical studies indicate that bevacizumab can be used in patients with ovarian cancer, even though the off-label indications of the drug do not currently include this use. In particular, Richmod et al.12 assessed the efficacy of bevacizumab given in combination with gemcitabine plus carboplatin and compared the results of their trial with the information previously published for patients given gemcitabine plus carboplatin without bevacizumab.14 The findings of Richmod's study show a median progression-free survival (PFS) of 12 months, whereas the median PFS expected in patients treated without bevacizumab has been reported to be 8.6 months.15 Hence, the clinical benefit attributable to bevacizumab is 3.4 progression-free months gained per patient.

For determining the value-based payment for this off-label treatment, both the trial-based approach and the individualized payment by results approach are shown below.

**Trial-based approach**

The clinical benefit attributable to bevacizumab is 3.4 months of PFS gained per patient. The economic equivalent attributed to this benefit is 8,500 EUR. According to the Q-TWIST approach, the economic equivalent attributed to one month gained of PFS is 2,500 EUR as opposed to 5,000 EUR attributed to each month gained of OS (overall survival). Since the survival gain is expressed in progression-free months, Equation 1 is re-written as follows:

\[
\text{SUGGESTED PAYMENT} = C_x + 2500 \times (\text{PFS}_x - \text{PFS}_y)
\]

Given that B is gemcitabine plus carboplatin, the value of C, can be assumed to be 4,141 EUR/patient according to current drug prices in Italy (see Appendix for details).

Hence, Equation 3 yields:

\[
\text{SUGGESTED PAYMENT} = 4,141 + 2500 \times 3.4 = 12641 \text{ EUR/patient}
\]

When—in case of combination therapies—the innovative combination treatment A differs from the reference treatment B only for the presence of one adjuvant drug (e.g. A=drug1+drug2 and B=drug2), the analysis can be simplified by omitting the agents that are present both in A and in B to facilitate the calculation. The analysis is therefore redesigned by comparing the adjuvant drug vs nothing; for example, the comparison of A=drug1+drug2 vs B=drug2 is re-written as drug1 vs nothing.

If one assumes that the total cumulative dose of bevacizumab is 10,400 mg/patient, the payment described above corresponds to a maximum price of 1,50 EUR/mg attributable to bevacizumab (where 1,50 EUR/mg is obtained from 12,641 EUR divided by 8,400 mg), that proves to be much lower than the current real price of bevacizumab (336 EUR/mg). Hence, bevacizumab used for this off-label indication should be paid at less than half of its current price.

**Individualized payment-by-results approach**

The example presented herein is based on the data of a single hypothetical patient who is assumed to be treated with a total cumulative dose of 12,000 mg of bevacizumab (which translates into a real expenditure of 40,312 EUR). Also in this case, C, = 4,141 EUR/patient. For this patient, the real expenditure for bevacizumab is assumed to be 42,000 EUR while the progression free survival is assumed to be 18 months (which is somewhat better than the median value found in Richmod's trial).
Since the survival gained is expressed in progression-free months, Equation 2 becomes:

\[
\text{PAYOUT} = (\text{REAL EXPENDITURE})_n \times \left[ C_0 + C_1 \times \left( 1 - \frac{e^{-C_2 \times D}}{e^{-C_2 \times D} + 1} \right) \right]
\]

In the case of the hypothetical patient considered in this example, the calculation proceeds as follows:

\[
\text{PAYOUT} = \frac{42000 \times [14114 + 2500 \times (18 - 6.6)]}{14359} = 27641 = 14359 \text{ EUR}
\]

In operational terms, the real expenditure for this patient is 14,359 EUR is initially incurred in full by the payer. Then, on the basis of the outcome observed in the patient, the manufacturer is requested to give 14,359 EUR as a payback.

This approach has already been proposed for innovative medical devices characterized by limited information in terms of clinical effectiveness, more importantly, this strategy—with minor modifications—is already being used in Italy for handling the payback of some on-label uses of oncology drugs. Its disadvantage is that a monitoring system (e.g., generally a web-based archive) must be set up to follow-up the outcomes of individual patients.

EXAMPLES OF APPLICATION

To describe the application of our procedure in both of its versions, Tables 1 and 2 report some examples of application that we have selected from the 2010 off-label oncology drug list of the Region of Tuscany covering a total of 184 off-label indications. Among these, we extracted only those drugs characterized by high budget implications and included for this reason in a national program of individual patient monitoring (called “Progetto AIFA-ONCO”) started in 2007 by our national regulatory agency.

Table 1 describes one example of application of the trial-based approach, while Table 2 shows two examples of the individualized approach.

It is noteworthy that the suggested payment of 14,359 EUR per patient for gefitinib (Table 1) is very close to the final agreement of 12,200 sterling pounds per patient made at the end of May 2010 in the UK (for this drug).

Of course, in choosing between the trial-based approach and the individualized approach the crucial factor is the availability or unavailability of robust efficacy data for Treatment A. When this information is available, the trial-based approach is operationally much simpler, and so it should probably be preferred. When this information is unavailable or shows a smaller degree of certainty, the evidence-based approach is not sufficiently reliable, and so the individualized approach becomes the best option.

The individualized payback-based approach relies on paybacks mainly for reasons of practical applicability, but its conceptual framework is extremely simple, when a patient treated with the innovative drug reaches the median survival expected with the “old” treatment, the manufacturer starts to be paid on a monthly basis at a rate of 5000 EUR per month in the case of overall survival and 2500 EUR per month in the case of progression-free survival. Of course, no payment is due to the manufacturer in those cases where the patient’s survival does not reach the median survival expected with the old treatment.

According to this conceptual framework of the individualized approach, the examples in the two tables show that each manufacturer could receive 5000 EUR for every month lived after the 15th month by a lenalidomide-treated patient; 2500 EUR for every month without progression lived after the 4th month by a bevacizumab-treated patient, and 2500 EUR for every month without progression lived after the 5th month by a gefitinib-treated patient, respectively.

The example of rituximab in Waldenström’s macroglobulinemia shows a poor degree of acceptability on the side of the manufacturer: in fact, 5000 EUR could be treasured by the manufacturer for every month lived after the 6th month by a rituximab-treated patient, but it is unlikely that the manufacturer could wait so long to receive the payment for the treatment.

CONCLUSION

This paper is the first attempt to set up a uniform method for handling the payment of off-label oncologic treatments based on clinical benefit. The method proposed in this paper is essentially an application of cost-effectiveness analysis for calculating a value-based price for off-label drugs.

Our proposal has some limitations. As already mentioned in the introduction, the absence of robust effectiveness data for off-label indications exposes the payer to the risk of overestimating, in some cases, the drug’s price. This risk is however...
TABLE 1 - Example of application of the trial-based approach. All details concerning the dosing regimens presented herein are reported in Appendix 1.

<table>
<thead>
<tr>
<th>Off-label indication</th>
<th>Innovative treatment (A)</th>
<th>Reference treatment (B)</th>
<th>C0 (EUR/patient)</th>
<th>Clinical endpoint measured as:</th>
<th>Expected outcome for treatment A</th>
<th>Expected outcome for treatment B</th>
<th>Incremental benefit</th>
<th>Ratio between real payment, per patient and suggested payment, per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non small cell lung cancer (with EGFR biomarker positivity)</td>
<td>First-line treatment with gefitinib 24</td>
<td>Carboplatin plus paclitaxel 24</td>
<td>8525</td>
<td>PFS</td>
<td>8.64 mo/patient</td>
<td>6.32 mo/patient</td>
<td>2.32 mo/patient</td>
<td>17083/14325= 1.19</td>
</tr>
</tbody>
</table>

Abbreviations: PFS = Progression-free survival

TABLE 2 - Two examples of application of the individualized payment-by-results approach. All details concerning the dosing regimens presented herein are reported in Appendix 1.

<table>
<thead>
<tr>
<th>Off-label indication</th>
<th>Innovative treatment (A)</th>
<th>Reference treatment (B)</th>
<th>C0 (EUR/patient)</th>
<th>Clinical endpoint</th>
<th>Outcome for treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic syndrome</td>
<td>Lenalidomide 25</td>
<td>Best supportive care 25</td>
<td>0 (no specific therapy)</td>
<td>OS</td>
<td>15 mo/patient</td>
</tr>
<tr>
<td>Waldenstrom’s macroglobulinemia</td>
<td>Rituximab 25</td>
<td>Chlorambucil 26</td>
<td>238</td>
<td>OS</td>
<td>65 mo/patient</td>
</tr>
</tbody>
</table>

Abbreviations: OS = Overall survival

likely to be minimized over time as more effectiveness data become available. The same problem however arises from the determination of the price for on-label indications.21,22

From a methodological point of view, our analysis was conducted by using the Q-TWIST method, which is widely used in the literature.14,15 This simplification is due to the difficulty in finding quality of life scores. Cost associated to therapy and cost of disease from hospitalization have not been included in the analysis, but this is a point to subject future improvement.

In conclusion, off-label indications are the “precursors” of innovative labeled indications, and so our choice to selectively examine off-label treatments sets up a methodologic pathway that could hopefully be kept unchanged when the indication studied moves from off-label to on-label.

COMPETING INTERESTS: Although AMI is a member of the drug reimbursement committee of the Italian drug agency (AIFA), this letter reflects his personal views.

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A UNIFORM PROCEDURE FOR REIMBURSING THE OFF-LABEL USE OF ANTI-NEOPLASTIC DRUGS ACCORDING TO THE VALUE-FOR-MONEY APPROACH

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