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METHODS

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A new payment-by-results method for determining the fair price of new oncological drugs

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ABSTRACT

The high prices of new cancer drugs are likely to undermine national health services sustainability. As a solution to this problem, the "payment-by-results" method was proposed and nowadays this approach is commonly implemented by national drug agencies: the drug manufacturer is set to refund to the National Health Service the price of the drug if the benefits expected for the patient are not achieved. Based on the payment-by-results approach, we developed a new and easy to implement model, that can set a fair price, so that neither industry, nor National Health Service can obtain an undue gain. Obviously, this price can be modified by adjusting refund amounts to new healthcare and market conditions.

Keywords: Payment-by-results, Progression-free survival, Overall survival, Survival distributions

Introduction

Because of the high prices of new oncological drugs, their approval by regulatory agencies may undermine the sustainability of the National Health Service (NHS). Furthermore, the average benefit for the patient is often moderate: the most common index to measure it, that of the incremental progression-free survival (PFS), ranges from some weeks to a few months when the new drug is compared with the standard therapy, depending on the tumor type and stage. The PFS seldom translates into a significant overall survival (OS) improvement, in part because the control patients are allowed to cross to the new treatment when, after an interim analysis, the experimental therapy has been shown to be more effective than the standard therapy in terms of PFS.

All stakeholders are aware of this issue. In practice, drug companies are trying to characterize patients according to genetic markers to maximize the efficacy of new drugs, while regulatory agencies and NHSs are trying to define new criteria to link drug prices to the real-world effectiveness shown in individual patients. Nowadays, among these criteria, payment-by-results seems to be the preferred method: payments are made by the NHS to the drug manufacturer only for patients in whom the drug is found to be effective. This criterion is controversial also because it is difficult to assess when a treatment is effective; in practice, in oncology, this assessment is based on continuous variables (PFS and OS), making it necessary to select a cutoff. This choice is affected by subjective factors, which is likely to cause conflicts between industry and NHSs.

The aim of this study was to develop a model for determining fair and equitable prices for new drugs in each patient, based on results achieved, so that neither the NHS nor the manufacturer achieve any unfair economic benefits. Thereafter, this price can be increased or decreased, according to the real market and health care conditions.

Methods

Let N be the new drug, S the standard therapy and N and S were already compared – in accordance with regulatory Agencies requirements – in a large, randomized parallel study where both the greater efficacy of N and a similar tolerability were demonstrated. Let f(S) and f(N) be the density functions of PFS for the standard treatment and for the new drug, respectively, with median Me(S) and Me(N): Me(N) > Me(S). Let Pt_0 be the patient in whom the efficacy is assessed. For instance, we hypothesize that Me(S) = 6 months, and Me(N) = 9 months; Figure 1 displays the density functions. In this figure, the vertical line in bold is the result observed for Pt_0 – i.e., PFS_0 (in the numerical example, 10 months).

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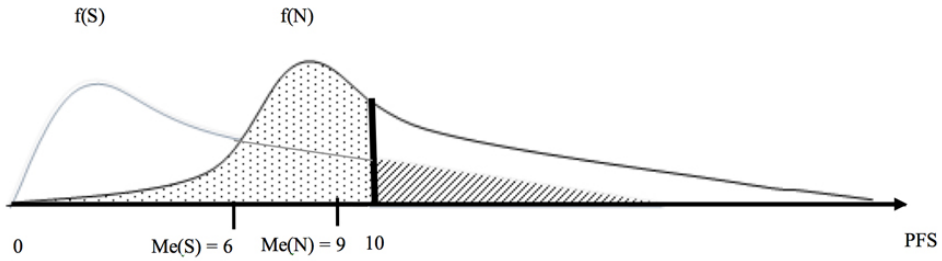

Fig. 1 - Density functions of PFS for standard therapy (S) and new drug (N). Let the progression-free survival (PFS) observed in patient Pt_0 be equal to 10 months. The dotted area in f(N) is a measure of the effectiveness of the new drug; the shaded area in the tail of f(S) is the probability of obtaining with the standard therapy a result equal or superior to that observed.

Net measurement of effectiveness

The efficacy is measured by PFS. Therefore, the area under the curve f(N) to the left of PFS_0 – i.e., $P_1 = P(PFS \leq PFS_0/N)$ – that is, the probability to obtain a value of PFS inferior or equal to that observed for the patients treated with the new therapy, is again a measurement of effectiveness because it is a monotonically increasing function of PFS and, from a statistical point of view:

- P_1 is equal to zero if and only if PFS = 0. In fact, if PFS = 0, then $P_1 = 0$; and vice versa, if $P_1 = 0$, then PFS = 0.
- As PFS increases, P_1 also increases (see the shaded area in Figure 1).

It should be noted, however, that, whatever is the outcome observed for the patient Pt_0, this could also be achieved with the standard therapy. Therefore, the measurement of effectiveness P_1 should be adjusted for the probability to obtain a result not inferior to that observed using the standard therapy – i.e., $P_2 = P(PFS \geq PFS_0/S)$ (see the shaded area in Figure 1).

Example. Let $P_1 = 0.6$ and $P_2 = 0.1$: if the new therapy had been administered, there would be a 60% probability of obtaining a result not greater than that observed (measurement of effectiveness of the new drug); in contrast, if the standard therapy had been administered, there would still be a 10% chance of obtaining a PFS value superior or equal to that observed.

We can estimate the effectiveness of N relative to S by means of the difference $(P_1 – P_2)$, considering the result that could be obtained even with standard therapy (in the example, $P_1 = 0.6$ and $P_2 = 0.1$: the new treatment has a "net" measure of efficacy of 50%, i.e., 0.6 – 0.1).

Costs

First of all, we hypothesized that the industry will supply in advance the drug that will be reimbursed by the NHS on the basis of the effectiveness demonstrated in each patient. The other two possible situations – i.e., that the NHS pays the whole price of the drug, and subsequently the industry makes a reimbursement to the NHS on the basis of the effectiveness demonstrated in each patient, which is the current practice; or that the drug is tested vs. a placebo, when administered in addition to the standard treatment – will be considered in the Discussion.

Let us consider the patients who given their conditions are eligible to receive a treatment, either the standard therapy or the new drug, and that, moreover, this latter treatment has already demonstrated a median PFS greater than that obtained with the standard therapy.

The patient Pt_0 receives the new drug. Let us denote with CN and CS the acquisition costs of the new treatment and the standard therapy, respectively, where CN > CS. The equitable price to be reimbursed to the industry (CR) for the patient Pt_0 is equal to the cost of standard therapy, CS (as the patient, however, requires a treatment), plus the product of the difference in effectiveness $(P_1 – P_2)$ and the difference between the costs (CN – CS):

$$CR = CS + (CN – CS) \times (P_1 – P_2), \quad [1]$$

where we assume that the second term of the sum is equal to zero if $(P_1 – P_2) < 0$; in this case, and when $(P_1 – P_2) = 0$, only the cost of the standard treatment should be reimbursed to the industry.

(Examples). Further we assume that CS = 100 euros and CN = 400 euros.

a) If $P_1 = 0.6$ and $P_2 = 0.1$ (as in the example given above), the NHS should reimburse CR = 100 + 300 x 0.5 = 250.
b) If the observed result was $PFS_0 = 1$ month, and, for example, $P_1 = 0.1$ and $P_2 = 0.90$, only the cost of the standard treatment should be reimbursed, because the difference $(P_1 – P_2)$ is negative.
c) If the observed result was $PFS_0 = 12$ months, and, for example, $P_1 = 0.95$ and $P_2 = 0.01$ (if we had administered the standard therapy, however, a result not inferior to that observed would have a 1% chance), then the price to be reimbursed would be equal to CR = 382 euros (not far from the full price).
d) If $PFS_0 = 18$ months, and, for example (approximately) $P_1 = 1$ and $P_2 = 0$, the price that the NHS should reimburse to the industry would be the full price of the drug (400 euros).

Parameters estimation

It is easy to use the method described above because in the articles reporting the results of the comparison between the new drug and the standard therapy, the two curves for PFS are generally reported. These two curves (one for the new drug, the other for the standard treatment) have on the x-axis the possible values of PFS (we use PFS* to indicate the generic value of PFS), and on the y-axis the proportion of patients who, for each value of

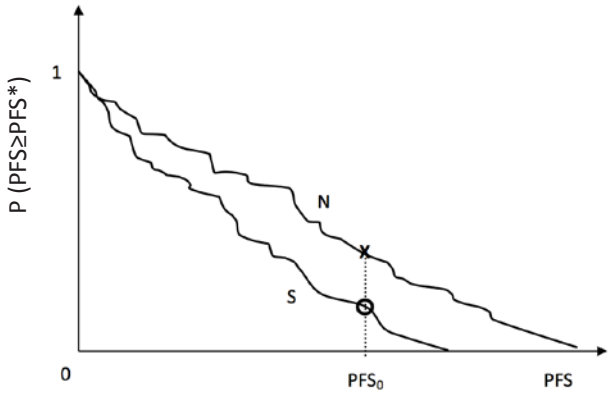

Fig. 2 - Progression-free survival (PFS) for the new drug (N) and standard therapy (S), where, in P(PFS≥PFS*), PFS* indicates any value of PFS between 0 and the observed maximum of PFS.

PFS, have had a PFS not inferior to that considered – i.e., P(PFS ≥ PFS*).

For example, in Figure 2 we display the two curves for PFS, similar to those that would be published in the articles reporting the clinical evidence. Let us consider the value obtained for the patient Pt_0 (i.e., PFS_0): we draw a parallel line to the y-axis passing through this point. This parallel intercepts the two curves at the points that, in Figure 2, are marked with a cross ('X') for the new drug and a circle ('O') for the standard treatment. These two ordinates are the estimations of the probability to observe a PFS not inferior to that obtained – i.e., $P(PFS \geq PFS_0)$.

Therefore, P_2 can be immediately read in this graph (circle). Instead, it is $P_1 = 1 - P(PFS \geq PFS_0/N)$, where, in Figure 2, $P(PFS \geq PFS_0/N)$ is indicated by the cross (X).

To make the procedure more understandable, we can apply it to a concrete case. Let us assume that a patient has obtained a PFS of 10 months (= PFS_0). We report this value on the horizontal axis of the graph of the two curves for PFS, N (new drug) and S (standard therapy), as published among the results of the clinical trial being considered.

The line parallel to the vertical axis passing through PFS_0 intercepts the two curves at the points that in Figure 2 are marked with a cross for the new drug and with a circle for the standard treatment. By drawing two lines parallel to the x-axis passing through these points we can read on the y-axis the values corresponding to these points (i.e., the circle and the cross). This is made easier by the numerical scale that is often given on the vertical axis.

These ordinates have the following meanings (see the legend on the y-axis in Figure 2):

- $P(PFS \geq PFS_0/N)$ (cross 'X')
- $P(PFS \geq PFS_0/S)$ (circle 'O')

representing the probability to observe a result equal or superior to that obtained using the new drug or the standard therapy, respectively.

Let us assume that values read in the graph are $P(PFS \geq PFS_0/N) = 0.4$ and $P(PFS \geq PFS_0/S) = 0.1$.

Consequently the value of 0.1 is directly P_2. To obtain $P_1 = P(PFS \leq PFS_0/N)$ – that is, the measure of the new drug effectiveness – we should subtract to 1 the probability read in the graph, corresponding to the cross (X), i.e., $P_1 = 1 - 0.4 = 0.6$. Therefore, the net measure of effectiveness of the new drug, expressed in probabilistic terms, is $P_1 - P_2 = 0.6 - 0.1 = 0.5$.

Discussion

Everything started with bortezomib (Velcade®), a protease inhibitor, for the treatment of multiple myeloma. In Great Britain, the National Institute for Health and Clinical Excellence (NICE; now National Institute for Health and Care Excellence), on the basis of a cost-effectiveness analysis, refused to recommend bortezomib to the UK National Health Service (NHS) because of its high price in relation to its low mean benefit for the patients (1). The manufacturer, Johnson & Johnson, rather than reduce the price, offered to reimburse the NHS drug sales for all patients who did not show a clinically satisfactory response. Since then, payment-by-results has become increasingly widespread, despite its shortcomings. However, the benefit for the industry is clear: all patients will be treated with the new therapy, and the industry will have high revenues, given that the drug is sold at full price; only later the drug manufacturer would reimburse the NHS for any clinical failure with procedures agreed with the NHS.

Currently, in Italy, there are several new oncological drugs whose price is fixed according to the payment-by-results criterion. For example:

- afatinib for first-line treatment of metastatic lung cancer with EGFR mutation: if during the first 6 months after starting treatment, the patient shows any progression of the disease, the manufacturer reimburses the full price of the drug; if the progression is observed after 6 months, the cost is paid entirely by the NHS;
- aflibercept in second-line treatment of metastatic colon cancer: if within 2 months, progression is observed, the manufacturer reimburses the whole price of the drug.

In this situation – i.e., when NHS pays the full price of the new drug, and industry reimburses it on the basis of any effectiveness shown – our model still applies: the industry will reimburse the NHS an amount equal to the difference between CN (already paid by the NHS) and CR (determined as above). In other words, the producer has already received CN, while it should have received CR; therefore, the industry should reimburse the NHS with CN – CR.

Sometimes the new drug is tested vs. placebo in addition to a standard therapy that all patients (both arms) receive. In this situation, setting the cost of placebo to zero, the expression [1] is transformed into

$$CR = CN \times (P_1 - P_2)$$

Obviously, the method remains valid even if the formal endpoint considered is OS instead of PFS. Unfortunately, in most cases it is not possible to assess OS, because when, at an interim analysis, it is proven that PFS is significantly higher for the new treatment, patients in the control group have the opportunity to receive the new therapy (crossover), based on ethical reasons that, in our opinion, are questionable because it is almost never proven that the PFS is a surrogate endpoint of OS (i.e., that an increase in PFS translates into an improved OS) and, therefore, PFS can only be considered an intermediate endpoint of OS (2).

But there is another reason why we choose to focus on PFS instead of OS: if results of a well-planned and well-conducted study, show a difference in the median OS that is similar to that reported in the example (9 vs. 6 months), then for ethical reasons related to the fact that a 50% increase in median OS in patients with a poor prognosis is not to be considered negligible, we should adopt the new treatment, regardless of its cost.

Moreover, a fair price as determined above could be varied, up or down, on the basis of an agreement between those who allocate health care resources and the manufacturer of the drug; this, however, falls in the domain of negotiation, which is eminently political, and into which, therefore, it does not seem appropriate to delve here. However, even in such cases, our model is useful because it allows us to make more transparent the mechanism by which the real price of the drug is formed.

With regard to the high costs of new oncological drugs, compared with their frequently modest efficacy, there is a growing concern about the sustainability of NHSs due to the explosive growth in pharmaceutical spending. Because of this situation, researchers proposed raising the efficacy threshold required for introducing a new drug into clinical practice. This stimulated a broad debate involving all stakeholders and entailing ethical issues, which makes irreducible the positions. In contrast, our method does not refer to a mean value derived from the experimental results of clinical studies, but is based on actual practice – that is, the demonstrated efficacy in individual patients. This avoids any controversy regarding the reproducibility of results of clinical studies in clinical practice and the modest clinical relevance of the new drug, because this approach allows us to reimburse the industry based on the demonstrated effectiveness in each patient: the cost variability from patient to patient in itself encompasses any other effect, which allows us to consider this approach to be not only practical but also fair, as it rewards only the most effective drugs.

Disclosures

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