

Gene Therapies A Burning Pharmacoeconomics Issue

XI Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica

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Introduction What are Gene Therapies

Somatic gene therapy: is performed on the somatic cells of an individual, so that the modifications that involve therapy only take place in this specific patient.

- 1. In vivo therapy: cell transformation takes place within the patient. It consists of administering to the patient a gene through a vehicle (for example a virus), which must locate the cells to be infected. The problem with this technique is that it is very difficult to get a vector that locates exclusively the target cells.
- 2. Ex vivo therapy: the cell transformation is carried out from a biopsy of the patient's tissue and then the transformed cells are transplanted. As it happens outside the patient's body, this type of therapy is much easier to carry out and allows a greater control of the infected cells.

Introduction Recent examples

| FDA News Release | | | | | | | |
|--|---------|-------------|----------|---------|--|--|-------------------|
| FDA approval brings first gene therapy to the United States | | | | | | | |
| CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia | | | | | | | |
| f SHARE | Y TWEET | in LINKEDIN | 🔞 PIN IT | M EMAIL | | | 0000 |
| The price of this treatment: 475, patient (Novartis); 373,000\$ (Gil | | | | | | | 000\$ per ead) |
| For Immediate August 30, 2017 Release | | | | | | | |

FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mutations in a specific gene

| | f share | y tweet | in LINKEDIN | O PIN IT | EMAIL | | |
|---------------|----------------|---------|-------------|-----------|-------|---|-----|
| For Immediate | | | Dec | ember 19, | 2017 | The price of this treatment: 850,00 for both eyes | 0\$ |
| Release | | | | | | | |

Introduction What is Immunotherapy

It is a treatment that uses certain parts of a person's immune system to fight diseases such as cancer.

It can be done in a *couple of ways*

Stimulating your own immune system to work harder or smarter to attack cancer cells Inhibiting those factors that are impeding the body's immune response against the tumor

Immunotherapy The costs

The rising cost of cancer

The average monthly cost of newly approved cancer drugs (in 2013 U.S. \$)



Source: Center for Health Policy & Outcomes, Memorial Sloan Kettering Cancer Center

Immunotherapy The costs

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2016



Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

Cost-effectiveness studies

What is in the literature?

The Value of New Cancer Therapies Cost-effectiveness studies

| Study & year of publication | Drug(s), disease, & treatment setting | Number of studies included | Results | Authors' Conclusion |
|-----------------------------|---|----------------------------------|--|--|
| Parkinson et al (2014) | Trastuzumab Her2 + MBC treatment containing trastuzumab versus a comparator (C/T, hormonal therapy, or BSC) | 15 | 1st line: ICUR: \$47,332 - 186,000/QALY; 2 nd line: ICUR: \$77,476/QALY | "None of the evaluations reported an ICER in the range that trastuzumab would be considered cost-effective" "There were numerous drivers of the different conclusions regarding the cost-effectiveness of trastuzumab, many of which are due to judgments made by the authors when translating data from RCTs" |

The Value of New Cancer Therapies Cost-effectiveness studies

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|--------------------------------|--|----------------------------------|--|---|
| Papaioannou et al (2012) | Rituximab FL (a subtype of NHL) Rituximab + C/T vs C/T alone | 4 | ICUR (based on the author's own estimates of HTA reports) \$11,677 – 16,388/ QALY | "This assessment provides an indication of the cost-effectiveness of the addition of rituximab to CVP, CHOP and MCP in a UK setting" |
| Auweiler et al (2012) | Rituximab NHL Rituximab + standard C/T vs standard C/T alone | 14 | All ICER below country-specific threshold: \$9,836 –39,328/ QALY | "Adding rituximab to standard chemotherapy is considered a cost- effective treatment option for NHL" |

Cost-effectiveness studies

| Study & year of publication | Drug(s), disease, & treatment setting | Number of studies included | Results | Authors' Conclusion |
|--------------------------------|---|----------------------------------|---|--|
| Hoyle et al (2013) | Cet, Bev, Pan mCRC (after 1st line); Cet (mono- or combination C/T), Bev (combination with non- oxaliplatin C/T) and Pan (monotherapy) vs irinotecan- or oxaliplatin-based C/T or BSC | 5 | ICUR (based on the authors' own estimates of HTA reports) Cet vs BSC: \$144,543/QALY; Cet + irinotecan vs BSC: \$129,794/QALY; Pan vs BSC: \$221,239/QALY; Bev: not modeled | "used for third- and subsequent-line treatment relative to best supportive care, cetuximab plus best supportive care, cetuximab plus irinotecan plus best supportive care and panitumumab plus best supportive care are effective but not cost- effective if a decision threshold of £20,000 per QALY or £30,000 per QALY is used." |

Cost-effectiveness studies

| Study & year of publication | Drug(s), disease, & treatment setting | Number of studies included | Results | Authors' Conclusion |
|--------------------------------|---|----------------------------------|--|---|
| Lange et al (2014) | Cet, Bev, Pan mCRC various combinations | 15 | ICER/ICUR Bev plus C/T vs C/T (1 st line): \$1,047 - \$149,614/LY; Bev + C/T vs Cet + C/T (1 st line): \$19,893/LY; Cet (+/- C/T or KRAS testing) vs other treatment (conventional or BSC or Cet without KRAS testing): \$21,033 - 2,932,767/LY; \$37,363 - 416,648 /QALY; Pan vs BSC: \$41,812 - 269,649 /QALY; Different treatment sequences: \$170,896 -243,096/LY | "The treatment with bevacizumab, cetuximab and panitumumab is mainly considered to be not cost- effective in patients with mCRC. However, testing for Kirsten ras oncogene (KRAS) mutation prior to the treatment with cetuximab or panitumumab is found to be clearly cost-effective compared to no testing " |

The Value of New Cancer Therapies Cost-effectiveness studies

- Systematic reviews regarding cost-effectiveness have been performed since 2012 for **one-third** (5/16) of agents (rituximab, trastuzumab, bevacizumab, cetuximab and panitumumab)
- Most (4/5) of these agents were considered as **not costeffective** in the systematic reviews with the noted exception of rituximab which has revolutionized the field of lymphoma.

The Value of New Cancer Therapies Cost-effectiveness studies

Other recent literature

| Study & year of publication | Objective | Number of studies included | Results | Authors' Conclusion |
|-----------------------------|--|----------------------------------|--|--|
| Guglielmo A (2018) | Review of economic evaluations on diagnosis of inherited colorectal cancer (CRC) syndromes and genetic tests for the detection of mutations associated with response to therapeutics | 20 | (a) Screening strategies among CRC patients were more effective than no screening; (b) All the evaluated interventions were cost-saving for certain willingness-to-pay (WTP) threshold; and (c) All new CRC patients diagnosed at age 70 or below should be screened | High level of uncertainty on the cost-effectiveness of genetic evaluations in CRC: Major research is required in order to assess the best combination among detection tests, type of genetic test screening and targeted- therapy. |

Acceptability Thresholds

20.000-30.000 £/QUALY The only explicit threshold NICE, 2008



50.000 US\$ / QUALY

Annual cost of dialysis for patients with chronic renal failure. since 1982. (Without adjustments for inflation).



20.000 - 100.000 CAN\$ / QUALY

Laupice et al. Canada 1990



50.000 - 80.000 € / QUALY

Boersma, C., Broere, A., & Postma, M. J. (2010). Quantification of the Potential Impact of Cost-effectiveness Thresholds on Dutch Drug Expenditures Using Retrospective Analysis. Value in Health, 13(6), 853-856.



500.000 SEK / QUALY

Hultkrantz, L., & Svensson, M. (2012). A comparison of benefit cost and cost utility analysis in practice: Divergent policies in Sweden (No. 2012: 5).



21.000 - 24.000 € / QUALY

Report commissioned by the Ministry of Health to the Evaluation Service of the Canary Health Service; 2015

Valor Monetario de un Año de Vida Ajustado por Calidad: Estimación empírica del coste de oportunidad en el Sistema Nacional de Salud

Informes de Evaluación de Tecnologías Sanitarias SESCS

INFORMES, ESTUDIOS E INVESTIGACIÓN





Gobierno de Canarias

- Vallejo-Torres L,
- García-Lorenzo B,
- Castilla I,
- Valcárcel Nazco C,
- García-Pérez L,
- Linertová R,
- Serrano-Aguilar P.



La Regulación del precio de los medicamentos en base al valor

Joan Rovira Forns Pedro Gómez Pajuelo Juan del Llano Señarís EVALUACIÓN, FINANCIACIÓN Y REGULACIÓN DE LOS MEDICAMENTOS INNOVADORES EN LOS PAÍSES DESARROLLADOS



Which metrics Are appropriate?

Cost effectiveness results are mostly negative...

But are we measuring Response properly

Which metrics Are appropriate?

- Immunotherapy has the potential ability to obtain "long survivors".
- It induces a new pattern of antitumor response that may not be detected by WHO or RECIST criteria (which takes the Median into account).

Which metrics Are appropriate?

Median Overall Survival may not be the best End-point for therapies with potential long-term benefit:

Median VS Mean: The Mean includes patients who survive above the Median (prolonged drug benefit)

Which metrics Are appropriate?

- New response criteria is developed:
 - Immune-Related Response Criteria (irRC)
 - "Cure Fraction" (Proportion of patients who survive and no longer present or experience that higher mortality rate caused by neoplastic disease)

Which metrics are appropriate?

Global Survival: WHO / RECIST vs. ir RC Criteria



Figure 3. Immune-related response criteria identify survivors among 227 patients enrolled in phase II studies of ipilimumab 10 mg/kg monotherapy that would have had progressive disease according to modified World Health Organisation criteria [15]. Reprinted by permission from the American Association for Cancer Research: Wolchok et al. [15].

The Value of New Cancer Therapies Survival: Some of the latest results

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer Reck, Martin, et al, New England Journal of Medicine, October 2016, online



Non-Small Cell Lung Cancer: Latest publications

Last cost-effectiveness studies are getting better results for the Non-Small Cell Lung Cancer. ¿Why?

Taking into account only tested patients with positive outcome (companion diagnostics)

"A Cost-Effectiveness Analysis of Nivolumab versus Docetaxel for Advanced Nonsquamous NSCLC Including PD-L1 Testing." Matter-Walstra et al.

"selection of patients for Nivolumab on the basis of **test positivity improves** cost-effectiveness compared with Docetaxel."

"Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States" **Huang M. et al.**

"Pembrolizumab improves survival, increases QALYs, and can be considered as a cost-effective option compared to docetaxel in PD-L1 positive (TPS ≥50%) pre-treated advanced NSCLC patients in the US."

The Value of New Cancer Therapies The burning questions

Are medicines worth what pharmaceutical companies are asking for them...?

Is it really that hard to fix an affordable price...?

The concept of Optimal pricing

The issue of To ensure that pricing allows access pharmaceutical to patients and encourages pricing: continuing innovation, but does not overburden health care systems Optimal Pricing Its issues

Issues that make *Optimal Pricing's* setting **difficult** Pharmaceuticals are very R&D intensive

The effect of Insurances

The globality of pharmaceutical products

Optimal Pricing Its objectives



Static efficiency

Dynamic efficiency

Optimal Pricing In a Global Context

Optimal pricing problem has to be distinguished between:

Countries with universal insurance Countries without universal insurance

Optimal Pricing In a Global Context

Countries with universal insurance

Static and dynamic efficiency can be approximated if:

- Payers define ICERs unilaterally based on citizens' WTP
- 2. Manufacturers set prices
- 3. Payers **determine eligibility** for reimbursement

Countries without universal insurance

No external reference pricing + parallel trade constraints = **monopoly behaviors:**

> Prices set on a country's average WTP). But what if the country's incomes are very skewed? Pricing to the most affluent population segment.

Possible solution: Assuring the quality of generics would improve price competition, and so, **affordability**. **But patents last about 20 years...**

CANCER IMMUNOTHERAPY CHEET SHEET



Some products have many indications; some cancers have several immunotherapy products. The overview lets quickly identify which cancers have more than one immunotherapy product available and eyeball how many manufacturers are currently competing in that market.

Adequately rewarding Companies for their innovation is a **hot debate**. **Consequently, Gene Therapies Pharmacoeconomics have to be a Burning Issue**

Health Technology Assessment: Recent Normative



<u>Proposal to reinforce cooperation amongst Member States regarding Health Technology</u> <u>Assessment (HTA)</u> (**Brussels, January 31th 2018**):

- The proposed Regulation on Health Technology Assessment (HTA) covers **new medicines** and certain **new medical devices**.
- Provide the basis for **permanent and sustainable cooperation** at the EU level for joint clinical assessments in these areas.
- Member States will be able to use common HTA tools, methodologies and procedures across the EU, working together in four main areas:
 - 1. On joint clinical assessments focusing on the **most innovative health technologies** with the **most potential impact for patients**;
 - 2. On joint scientific consultations whereby developers can seek advice from HTA authorities;
 - 3. On identification of emerging health technologies to **identify promising technologies early**;
 - 4. On continuing voluntary cooperation in other areas. **Individual EU countries** will **continue** to be **responsible for assessing non-clinical** (e.g. economic, social, ethical) **aspects** of health technology, and **making decisions on pricing and reimbursement**.

Health Technology Assessment: Recent Normative



Justification

- Greater transparency will **empower patients**, by ensuring their access to information on the added clinical value of new technology that could potentially benefit them.
- More assessments could lead to effective, innovative health tools **reaching patients faster**. For national authorities it means being able to formulate policies for their health systems based on more robust evidence. Furthermore, manufacturers will no longer have to adapt to different national procedures.

Next steps

- The proposal will now be discussed by the European Parliament and the Council of Ministers.
- It is expected that once it is adopted and enters into force, it will become applicable three years later.
- Following the date of application, a further three-year period is envisaged to allow for a phase-in approach for Member States to adapt to the new system.

Conclusions

- 1. Anticancer drug costs may change substantially after launch. Regardless of competition or supplemental indications, there is a steady increase in costs of patented anticancer agents over time. New regulations may be needed to prevent additional increases in drug costs after launch. (http://ascopubs.org/doi/full/10.1200/JCO.2016.72.2124)
- 2. Redefine the way we measure: asset the real added value of immunotherapy.
 - Speak in terms of social perspective
 - More accurate measurement of effectiveness (real response, companion diagnostics, better ICER results)
- 3. Improvement of the allocation and efficiency of resources across the spectrum of cancer care, without forgetting the goal: improve survival and patients outcomes.

Last thoughts

FDA vs EMA. In Europe Health Systems are mainly public. USA is guided by market.

- Authorization is faster in FDA. EMA is more cautious.
- Price fixing in Europe is based in systems perdurability. In USA the company freely fix the price (public and private insurance companies bargain final price afterwards)

Dr. Polite (ASCO 2017): "Everyone gets paralyzed by discussions of drug value. And although value is hard to define and there is not one definition out there that is perfect, we are much further down the road than we were even 1 or 2 years ago. Once we can come to a consensus on the definition of drug value, we can test a number of strategies to reduce cancer costs, including new clinical efficacy endpoints, provisions for Medicare drug payment negotiation, and value-based payment pathways. It's not easy, but it can be done."

Josep Tabernero (El País, 5 Feb. 2018). "El precio de los medicamentos contra el cáncer lo marca el mercado y es un modelo equivocado. El precio de los nuevos fármacos "no tiene una relación proporcional con el beneficio que dan".



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Thank you

Dr. Juan E. del Llano-Señarís Director, Gaspar Casal Foundation President, Spanish Association for Health Technology Assessment Barcelona March 5th, 2018