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Biotechnology drugs and cancer
All that glitters is not gold

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abstract

Objetives: to review the efficacy, safety profile and costs of biotechnology drugs routinely employed in cancer patients. **Methods:** information published by the FDA and the EMA on pivotal trials which led to the approval of these drugs was evaluated. **Results and conclusions:** some biotechnology drugs have shown to be useful in the treatment of cancer patients. However, the majority present questionable efficacy, considerable adverse effects and are costly. It is convenient to demonstrate greater scientific rigor when approving or withdrawing these drugs. The public health services should consider selective financing of these drugs in terms of treatment benefits. **Key words:** biotechnology drugs, oncology, cancer, antineoplastic drugs.

Introduction

In the last few years, various drugs whose origin is not of traditional chemical synthesis have been commercialized. These drugs are obtained from biological systems or living organisms. For this reason, the common *in vitro* procedures include recombined DNA and direct injection of nucleic acids in cells or organelles.

The development of these drugs started in the early 1980s and commercialization in the 1990s. The use of these agents is increasing and it is almost certain that more drugs will be available on the market in the near future.

According to their mechanism of action, these drugs can be classified in various groups, mainly protein kinase inhibitors, selective mTOR inhibitors and monoclonal antibodies.

Among the **protein kinase inhibitors**, it is worth mentioning kinase tyrosine inhibitors. This enzyme contains numerous isoforms and regulates processes of proliferation, angiogenesis, and tumor metastases.

Among the **selective mTOR inhibitors** (target of rapamycin), the most commonly used drug is temsirolimus. The inhibition of mTOR activity provokes a detention of the cellular division cycle.

The cell membrane contains a series of receptors for various ligands such as the epidermal growth factor (EFGR) and the vascular endothelial growth factor (VEGFR). The stimulation of these receptors triggers some biochemical signals that produce cell proliferation while their inhibition presents antitumoral effects[1]. It is important to take into account the erbB family, composed of four different human epidermal receptors (HER), namely EFGR, HER-2, HER-3 and HER-4.

On the other hand, **monoclonal antibodies** are a group of drugs which are capable of recognizing an antigen determinant of some membrane structure of the tumor cell and produce its destruction[2].

The objective of this article is to evaluate the efficacy and safety profile of the common biotechnology antineoplastic drugs used in medical practice with regard to their main indications. The article also describes the economic impact on the Navarre Health Services (Spain).

Limitations of the article

This article has been carried out using the information available from the FDA and the EMA to approve these drugs. It is not a systematic review of each and every one of them, but offers a comprehensive vision of these drugs.

Primary endpoints of the clinical trials. What information on efficacy do we have?

When a patient receives the news that he suffers from cancer, the patient finds himself in a situation where his life is at risk. Therefore, the main concern of the patient is to "overcome the cancer." In these circumstances it is easy to understand the primary endpoint in a clinical trial in the cancer field is **overall survival,** that is the proportion of patients that stay alive at a given time after cancer therapy has been employed. The measurement is the *time from randomization to death due to any cause.*

In the case of tumors with slow evolution, follow up may be costly with regard to the evaluation of the possible differences of two treatments on the overall survival of these patients. In these cases, it is justified to employ surrogate endpoints such as **disease-free survival.** This is understood as the period between randomization and recurrence (organ affectation) or death. If one of the treatments under study shows that this period free of disease is increased with respect to the other treatment option, then it is inferred that the former therapy also increases overall survival. However, this could not be true in every case. In 1991 the FDA accepted another surrogate endpoint to approve the use of carboplatin for ovarian cancer. This is the **progression-free survival**, understood as the period from randomization to progression of the tumor or death of the patient. This endpoint is weaker than the former in inferring results with respect to future patient survival.

Finally, there is a series of surrogate endpoints that show low consistency and which do not offer very reliable information with regard to survival. These include **time to progression** (time between randomization and tumor progression, excluding death), **complete response** (disappearance of lesions, and presence of lymph nodes with a short diameter of less than 10 mm), **partial response** (reduction of over 30% of the sum of the diameter of the lesions), **objective response** (proportion of patients with a reduction on the size of the tumor equal or greater than a predefined value established by the researchers).

As we will see later, in the last few years the approval of biotechnology drugs in cancer is accelerating. The majority of the approvals however, are based on weak endpoints, with no reference to efficacy in terms of survival or clinically relevant results on improvement of survival.

The general poor quality of the information is not exclusive to the reports of the regulatory agencies. In a review of clinical trials on advanced breast cancer published by 8 high impact medical journals between 2000 and 2007 (n=58), it was found that only two presented the primary endpoint of survival and nearly 75% used inconsistent surrogate endpoints[3].

As we shall observe further ahead, experience tells us that surrogate endpoints in many occasions, do not serve to predict results of drugs under study with regard to overall survival.

Efficacy of drugs

Among the group of protein kinase inhibitors, the main active substances employed are: imatinib, dasatinib, erlotinib, lapatinib, nilotinib, sorafenib, sunitinib and gefitinib. Among the monoclonal antibodies, the most habitually prescribed agents include alemtuzumab, bevacizumab, cetuximab, panitumumab, rituximab, trastuzumab. The main mTOR inhibitor is temsirolimus.

One of the particularities of these drugs is that many of them have been approved by "a fast track procedure" introduced by the FDA in 1992. This system is reserved for those drugs directed at severe diseases or of vital risk that are not effectively managed with current treatments. This implies that their indication is approved based on results from phase II and/or data from composite endpoints, in the expectation of data on survival in the future.

In reality, these drugs are approved too quickly as soon as any beneficial effect is observed in secondary endpoints of dubious consistency. This provokes an abrupt suspension of the trial in many occasions, without any data on long-term survival that can orient us on the real efficacy of these drugs.

Many drugs have been approved based on surrogate endpoints that do not correlate with an increase in overall survival

Drugs with the best data available on survival or relevant endpoints

Sometimes a beneficial effect of a drug under study can be observed which continues over time, but does not reach statistical significance, possibly due to premature interruption of the study or low mortality associated with the disease, such as the case of chronic myeloid leukaemia. We have classified these drugs as "drugs with the best data on survival or relevant endpoints." Table 1 shows the relationship between the different biotechnology drugs according to their efficacy

Imatinib and chronic mieloid leukaemia

Imatinib (Glivec®, Gleevec®) is a drug that has shown proven efficacy in the management of chronic myeloid leukaemia (CML). It was developed primarily in the University of Portland (USA) with public funding from the National Institute of Health[4]. At the moment of its approval, there were follow-up data of clinical trials of up to 7 years, showing a 40% increase in the number of patients with complete hematological response with respect to standard therapy available at that time and an increase in overall survival of 3.1% ($p=0.07$)[5] (table 1). In pooled data from two trials on CML (n=876), a 10.9% ($p < 0.001$) increase was observed in overall survival compared to INF + citarabine after 42 months of follow-up[6].

Tabla 1. Eficacia de distintos medicamentos biológicos en el momento de su aprobación por la EMA.

	Drug	Comparator	Indication	Primary endpoint / others	Results	Duration
Drugs effective in some indications	Imatinib	IFN + ara-C	Chronic myeloid leukaemia	Complete hematological response Overall survival	Imatinib: 96.6% (95%CI, 94.7%-97.9%), n = 553 IFN + ara-C: 56.6% (95%CI, 52.4%-60.8%), n=553 Increase by 40% of patients with complete response after 7 years (p<0.001) Imatinib: 86.4% (95%CI, 83%-90%) IFN + ara-C: 83.3% (95%CI, 80%-87%) Increase by 3.1% in overall survival alter 7 years. (p=0.07)	7 years
	Rituximab	Add-on therapy Ciclophosphamide + Vincristin + Prednisolone	Follicular lymphoma	Progression-free survival Overall survival	Ciclophos+vicris+prednisolone: 14.7 months Ciclophos+vicris+prednisolone+rituximab: 33.6 months Increases progression-free survival by 18.9 months. Ciclophos+vicris+prednisolone: 71.1% Ciclophos+vicris+prednisolone+rituximab: 80.9% Increases overall survival by 9.8% after 4.4 years	4.4 years
	Cetuximab	Placebo	Locally advanced squamous cell cancer of the head and neck	Loco-regional control Overall survival	Cetuximab + radiotherapy: 24.4 months Radiotherapy: 14.9 months Increases loco-regional control by 9.5 months Cetuximab + radiotherapy: 49.0 months Radiotherapy: 29.3 months Increases overall survival by 19.7 months	5 years
	Trastuzumab	Add-on therapy Docetaxel	Metastatic breast cancer	Progression-free survival Overall survival	Docetaxel: 6.1 months (95%CI, 5.4-7.2) Docetaxel + trastuzumab: 11.7 months (95%CI, 9.2-13.5) Increases progression-free survival by 5.6 months Docetaxel: 22,7 months (95%CI, 19.1-30.8) Docetaxel + trastuzumab: 31.2 months (CI95%, 27.3-40.8) Increase in overall survival by 9.5 months	4 years
	Trastuzumab	Add-on therapy Paclitaxel	Metastatic breast cancer	Progression-free survival Overall survival	Paclitaxel: 3.0 months (95%CI, 2.0-4.4) Paclitaxel + trastuzumab: 7.1 months (95%CI, 6.2-12.0) Increases time to tumor progression by 4.1 months Paclitaxel: 17.9 months (CI95%, 11.2-23.8) Paclitaxel + trastuzumab: 24.8 months (CI95%, 18.6-33.7) Increases overall survival by 6.9 months	
Alternative drugs to the first line option	Dasatinib	Dasatinib (in imatinib resistant patients)	Chronic myeloid leukaemia	Partial and complete response % patients free of progression	Total patients: 63% (56-71) Imatinib resistant patients: 59% (50-68) Total patients: 80% (73-87) Imatinib resistant patients 77% (68-85)	2 years

				Overall survival	Total patients: 91% (86-96) Imatinib resistant patients: 89% (84-95) No significant differences in overall survival	
	Nilotinib	Nilotinib (in imatinib resistant patients)	Chronic myeloid leukaemia	Cytogenetic response Partial and complete response Overall survival	59% initially and 49% after 2 years Uncontrolled, open, unconcluded phase II trial 51% (46%-57%) 87%	2 years
Drugs of questionable efficacy in some indications	Imatinib	Placebo	Gastrointestinal stroma tumor (GIST)	Time to recurrence Overall survival	Imatinib: 75% patients with no recurrence after 38 months (95%CI, 30 – not estimable) Placebo: 75% patients with no recurrence after 20 months (CI95%, 14 – not estimable) HR = 0.398 (0.259-0.610), p<0.0001 Differences not significant in overal survival (data not published)	4 years
	Erlotinib	Placebo	Non microcytic lung cancer 2nd line	Overall survival (median)	Erlotinib: 6.7 months (5.5-7.8) Placebo: 4.7 months (4.1-6.3) 2-month median increase in survival	1 year
	Lapatinib	Placebo	Metastatic or advanced breast cancer HER2 (+)	Time to progression Overall survival	Capecitabin: 18.3 weeks Capecitabin + lapatinib: 23.9 weeks , p<0.01 Increase of 5.6 weekks time free of progression No significant differences in overall survival	1 year
	Sorafenib	Placebo Placebo	Hepatocellular Carcinoma Hepatocellular Carcinoma	Overall survival No primary endpoint specified beforehand	Sorafenib: 10.7 months Placebo: 7.9 months Increase of 2.6 months in overall survival Overall survival: Sorafenib: 6.5 months Placebo: 4.2 months Increase of 2.3 months in overall survival	1 year
	Sorafenib	Placebo	Advanced renal cancer	Overall survival	Sorafenib: 19.3 months Placebo: 15.9 months Increase fo 3.4 months in overall survival	2 years
	Sunitinib	Alpha Interferon	Advanced and/or metastatic renal cancer	Progression-free survival Overall survival	Sunitinib: 11.8 months Alpha Interferon: 5.5 months Increase of 6.3 months in time free of progression Sunitinib: 28.6 months Alpha Interferon: 23.7 months No significant difference, p=0.051	3 years

	Drug	Comparator	Indication	Primary endpoint / others	Results	Duration
	Sunitinib	Placebo	Gastrointesinal stroma tumor (GIST)	Progression-free survival Overall survival	Sunitinib: 6.65 months Placebo: 1.6 months Increase of 5 months free of progression Sunitinib: 18.2 months Placebo: 16.2 months No significant differences, p=0.306	2 years
	Temsirolimus	Interferon	Advanced renal cell cancer	Overall survival	Interferon: 7.3 (6.1-8.8) months (reference) Temsirolimus: 10.9 (8.6-12.7) months, p=0.02 Interferon + temsirolimus: 8.4 (6.6-10.3) months , n.s. Increase by 3.6 months in the overall survival with respect to alpha interferon (IPN vs TEM) and no increase in survival in the other comparison (IPN vs IPN+TEM)	3 years
	Alemtuzumab	Chlorambucil	Chronic myeloid leukaemia	Progression-free survival Overall survival	Alemtuzumab: 14.6 months Clorambucilo: 11.7 months Increase of 2.9 months in progression-free survival No data available	2 years
	Bevacizumab	Placebo	Metastatic colorrectal cancer	Overall survival	Of the 4 trials of EPAR, one did not find differences respect to placebo, the rest found that bevacizumab increased overall survival between 1.6 and 4.7 months	3 years
	Bevacizumab	Placebo	Non microcytic lung cancer	Overall survival Progression-free survival Overall survival	Carboplatin+paclitaxel: 10.3 months Carboplatin+paclitaxel+bevacizumab: 12.3 months Increase of 2 months in overall survival Cisplatin+gemcitabine: 6.1 months Cisplatin+gemcitabine+bevacizumab: 6.7 months Increase of 0.6 months in progression-free survival No significant differences in overall survival	1 year
	Bevacizumab	Placebo	Advanced and/or metastatic renal cancer	Overall survival Progression-free survival	Interferon + placebo: 21.3 months Interferon + bevacizumab: 23.3 months No significant differences in overall survival Interferon + placebo: 5.4 months Interferon + bevacizumab: 10.2 months Increase of 4.8 months in progression-free survival	2 years
	Cetuximab	Placebo	Metastatic colorrectal cancer (EGFR+) with wild-type KRAS gene	Overall survival	Cetuximab + FOLFIRI: 23.5 months FOLFIRI: 20.0 months Increase of 3.5 months in overall survival Cetuximab + FOLFOX4 FOLFOX4 No significant differences in overall survival Cetuximab + oxaliplatin+5-FU oxaliplatin+5-FU No significant differences in overall survival	1-2 years

					Cetuximab + irinotecan Irinotecan (trial registration number CA225006) No significant differences in overall survival Cetuximab + irinotecan Irinotecan (trial registration number EMR 62 202-007) No significant differences in overall survival
Irregular approvals by regulatory agencies	Erlotinib	Placebo	Pancreatic cancer	Overall survival	In July 2006 rejection of this indication. The company solicits a meeting with a new panel of experts, three of whom had important links to the company. The indication is approved.
	Bevacizumab	Placebo	Breast cancer	Overall survival	The FDA approves the indication of bevacizumab in breast cancer when in the primary endpoint (overall survival) the drug was no better than placebo. To do so, the primary endpoint was modified to progression-free survival (composite endpoint) a suggestion made by the pharmaceutical company. Two later trials did not find differences between bevacizumab and placebo in either survival freeof progressiona or overall survival. Finally it the indication was withdrawn by the FDA. The EMA only withdrew its indication in combined therapy with docetaxel, while maintained its use in association with paclitaxel.
	Panitumumab	Placebo	Colorectal cancer EGFR+ wild-type KRAS gene	Overall survival	No increase in overall survival. The EMA maintains the indication though.

Cetuximab and locally advanced squamous cell cancer of the head and neck

Cetuximab (Erbitux®) is indicated for the treatment of patients with squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease, or in combination with platinum-based chemotherapy for recurrent and/or metastatic disease.

In the case of locally advanced cancer in the report offered by the EMA, there is one trial that compares the concomitant administration of cetuximab with radiotherapy compared to only radiotherapy. The primary endpoint was loco-regional control, with an increase in 9.5 months in the cetuximab group (24.4 vs 14.9 months). The overall survival was measured as a surrogate endpoint and an increase of up to 20 months in survival was observed in the group under the drug (49 vs 29.3 months)[7]. This trial has been published in two different medical journals[8,9].

However the role of this drug in metastastic or recurrent disease is more questionable. In the EMA report there is a trial in which there is an increase in survival of 2.7 months (10.1 vs 7.4 months $p<0.05$) when platin-based chemotherapy is associated[7-10]. However a trial carried out by a cooperative group for this same indication did not find statistically significant differences between cetuximab and placebo in overall survival[11]. A better objective response rate was observed in the EFGR+ subgroup though no effect on overall survival was seen.

Trastuzumab and metastatic breast cancer

Trastuzumab (Herceptin®) is indicated for the treatment of patients with HER2 positive metastatic breast cancer. In addition to treatment with paclitaxel, it has been shown that there is an improvement in progression by 4.1 months and the overall survival is 6.9 months. When added to docetaxel, the improvement was 5.6 and 9.5 months respectively[12].

Further meta-analyses have confirmed the efficacy of this agent in this indication[13,14].

Rituximab and non-Hodgkin's lymphoma

Rituximab (MabThera®) is indicated in adults for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. The trials included in the EMA's report which justified the approval of this agent for the treatment of follicular lymphoma presented a duration of 18 and 53 months. It was observed that after 4.4 months of treatment, the progression-free survival increased by some 19 months and the proportion of patients alive increased by 9.8% (80.9% vs 71.1%, rituximab and placebo respectively)[15]. In further studies the efficacy of this agent has been confirmed on the long term (more than 4 years)[16,17].

Alternative drugs to the elective treatment option

Dasatinib and chronic myeloid leukaemia

Dasatinib (Sprycel®) is indicated in the management of chronic myeloid leukaemia (CML) and acute lymphoid leukaemia. The report issued on its approval contained hardly any information compared to imatinib, the elective option. While the latter presented trials with a 7-year follow-up period, dasatinib trials lasted for two years only. It was approved on the basis of the results from two open trials on CML in patients with intolerance or resistance to imatinib. The primary composite endpoint was complete and partial responses[18].

Dasatinib did not show any improvements in survival rates or any other hard endpoints in comparison to imatinib. However, there was a very higher proportion of patients with intolerance or resistance to imatinib, who showed a favourable response to dasatinib, which confers the latter a very interesting therapeutic role in these patients (Table 1).

In the only comparative trial between dasatinib and imatinib, the former showed a higher complete cytogenetic response rate after 12 months [77% (71%-82%) vs 66% (60%-72%), p= 0.007][19]. However there are no long-term data available.

Nilotinib and chronic myeloid leukaemia

Nilotinib (Tasigna®) is indicated in chronic myeloid leukaemia in cases of intolerance or resistance to any other agent including imatinib. Its approval was based on the results of an open, uncontrolled and incomplete phase II trial at the moment of approval. The primary endpoint was cytogenetic response, which was 59%. After 2 years, the response was 49%, with a survival rate of 87% at this moment[20].

This year, the trial giving way to the approval of the drug has been published[21]. There are no data on efficacy or safety in the long term. This drug can be considered as a last management option in the treatment of chronic myeloid leukaemia after imatinib and dasatinib.

Drugs of questionable efficacy in specific indications

Imatinib and Gastro Intestinal Stroma tumor (GIST)

While imatinib has shown efficacy in the management of chronic myeloid leukaemia, its efficacy in the treatment of gastrointestinal stromal tumor is questionable. It was approved by the EMA given the results of a clinical trial in which imatinib was compared to surgical resection of the tumor and the primary endpoint was time to recurrence. In 75% of the cases, patients under imatinib did not develop recurrence after 38 months while 75% under placebo were free of disease after 20 months. HR = 0.398 (0.259-0.610), p<0.0001). There were no significant differences in overall survival rates between placebo and imatinib[5]. Nor were there any further studies after the approval of this indication that showed efficacy with regard to the increase in overall survival with the drug.

The indication in unresectable or metastatic GIST with high risk of recurrence was approved based on the results of two uncontrolled phase II studies in which an improvement was observed in the "objective response" when compared with a historical control group.

However a recent study presented at a congress of the American Society of Clinical Oncology showed that after 3 years of treatment with imatinib, patients with high risk GIST who had undergone surgery improved significantly in overall survival and in disease-free survival in comparison with one-year of treatment. In this study 400 patients diagnosed with GIST and a high risk of recurrence, were randomly assigned to treatment with imatinib for 1 to 3 years after surgery. After a median follow-up of 54 months, the disease-free survival after 5 years was 66% in the group under treatment compared to 48% in the group under one-year treatment. The overall survival after 5 years was also greater in the group under treatment for 3 years (92%) compared to the one-year treatment group (82%)[22].

Erlotinib and non-small cell lung cancer

Erlotinib (Tarceva®) is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer with EGFR activating mutations. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR)-IHC negative tumors. The first-line agents in this indication include: gemcitabine, docetaxel, paclitaxel, vinorelvine y pemetrexed. It is also possible to associate bevacizumab or cetuximab, drugs which will be considered later.

The trial which led to approval of this drug evaluated the overall survival as the primary endpoint. The median in the group under erlotinib was 6.7 months (5,5-7.8) compared to 4.7 months (4.1-6.3) in the group under placebo. That is, the median survival increased by 2 months after adding erlotinib to treatment [23,24]. A clinical trial carried out later showed a very limited improvement in overall survival, around one month. Another two trials in which the primary endpoint was overall survival showed that the drug was not more effective than placebo[25,26]. When erlotinib was employed as maintenance therapy after chemotherapy, an increase in progression-free survival of one month [27]. This limited efficacy observed in the majority of the trials contrasts with the data published of a study in South East Asia in which erlotinib improved the overall survival by nearly 8 months (14.7 compared to 6.8 months) [28].

Lapatinib and advanced or metastatic breast cancer

Lapatinib (Tyverb®) is indicated for the treatment of patients with breast cancer, whose tumors overexpress HER2 (ErbB2) and which progresses after previous treatment that includes anthracyclins, taxanos and trastuzumab. It was approved on the basis of a clinical trial whose primary endpoint was time to tumor progression. The addition of lapatinib to capecitabine reduced the time to progression by approximately one month (23.9 vs 18.3 weeks, $p<0.01$). However, no differences in overall survival were observed [29].

Further trials confirmed the discrete results in time to progression. In two studies in which overall survival was evaluated, it was affirmed that there is a tendency to improvement, but there was no case shown where survival was prolonged with the addition of lapatinib [30,31].

Sorafenib and hepatocellular carcinoma

Sorafenib (Nexavar®) is indicated for the treatment of hepatocellular carcinoma and for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

The use of sorafenib in hepatocellular carcinoma was approved by the EMA based on the results from two clinical trials. In one of them, the primary endpoint was overall survival and time to symptomatic progression. The study was suspended early because pre-specified limits of efficacy were reached. Nevertheless, the improvement in survival was only 2.8 months (10.7 vs 7.9 months, sorafenib and placebo groups respectively). The other trial had no predefined primary endpoint. Overall survival, time to progression, time to symptomatic progression and safety were evaluated. The results of overall survival were similar to the previous study, with an improvement of 2.3 months in the group under treatment with sorafenib vs placebo (6.5 vs 4.2 months respectively)[32]. These two trials were later published in full [33,34].

Sorafenib and advanced kidney caner

The EMA report approves sorafenib in the treatment of advanced renal cancer, with reference made to two clinical trials, one in phase II and the other in phase III. The primary endpoint of the latter was overall survival and progression-free survival. An improvement in overall survival of 3.4 months was observed in the sorafenib group compared to placebo (19.3 vs 15.9 months respectively)[31]. This trial was later published in two different medical journals[35,36]. The results did not coincide exactly with those published by the EMA. The improvement in overall survival in the sorafenib group in the articles was somewhat lower (2.6 months, 17.8 vs 15.2 months respectively) than those in the EMA report (3.4 months), with no statistical significance.

Sunitinib and advanced renal cell carcinoma

Sunitinib (Sutent®) is indicated for the treatment of advanced/metastatic renal cell carcinoma in adults and for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumor (GIST) in adults after failure of imatinib mesilate treatment due to resistance or intolerance.

Studies on renal cancer available in the reports from the EMA consist of a phase II trial, another trial in phase III, and one open uncontrolled trial. In the phase III trial, the effects of sunitinib were compared to those of alpha-interferon and it was observed that sunitinib increased the progression-free survival (primary endpoint) by 6.3 months (11.8 vs 5.5 months)[37].Initially the results of the interim analysis were published[38], and later the complete data[39].

Sunitinib increased the median overall survival rate by 4.6 months with respect to interferon alpha (26.4 vs 21.8 months), [HR = 0.81 (0.66-0.99); p = 0.036]. Sunitinib showed better tolerance.

Sunitinib and Gastro Intestinal Stroma Tumor (GIST)

The indication for the management of gastrointestinal stroma tumor and in malignant unresectable form after failure with imatinib was obtained based on the results of a placebo-controlled clinical trial in which the primary endpoint was time to tumor progression. Sunitinib showed a slowing down in progression by 5 months, but did not show better results in relation to overall survival[36].

Temsirolimus and advanced renal cell carcinoma

The indication of temsirolimus (Torisel®) is based on an open clinical trial in which a comparison of the overall survival of untreated patients with renal cell carcinoma were given temsirolimus, interferon alpha or both. Temsirolimus increased the survival by 3.6 months vs interferon alpha (10.9 vs 7.3 months respectively). However, the combination of both drugs did not show any advantages in overall survival compared to interferon alpha in monotherapy. This therefore raises doubts on the findings related to the increase of survival with temsirolimus compared to interferon[40,41].

Alemtuzumab and chronic lymphoid leukaemia

Alemtuzumab (Mabcampath®) is indicated in the management of B- cell (CLL-B) chronic lymphoid leukaemia in cases where chemotherapy in combination with fludarabine is not adequate. In the open trial which led to this indication, an improvement in progression-free survival of 2.9 months was observed compared to chlorambucil (14.6 vs 11.7 months) There are no data on overall survival[42,43].

Bevacizumab and metastatic carcinoma of the rectum and colon

Bevacizumab (Avastin®) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum. Common antineoplastic drugs employed in this cancer include 5-fluorouracil (as monotherapy or in combination with levamisol or leucovorin), oral fluoropyrimidines (capecitabine and UFT), ralatitrexed, irinotecan and oxaliplatin. Bevacizumab has been tested as additional therapy to some of these drugs or their combinations.

In the report from the EMA there are 5 registered trials that justify its approval in this indication[44]. In four of them this agent was the first-line treatment of the tumor while in one it was the second line treatment option. The primary endpoint was overall survival and, in the four trials, the addition of bevacizumab prolonged survival by about 3 months[45,46,47], while in one trial no differences were observed compared to placebo[48].

This efficacy in overall survival observed in the studies provided by the company to approve the drug is very small in absolute terms. Moreover, no corroboration has been shown in further studies carried out. In one of them an increase in overall survival was observed in the group under bevacizumab similar to other trials (3 months)[49], but other four trials did not find differences on overall survival between the drug and placebo[50,51,52,53].

Bevacizumab and lung cancer

Bevacizumab (Avastin®), in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. In the EMA report there are two trials regarding this indication. One of them is an open trial in which the results on overall survival were evaluated with the addition of bevacizumab to the combination of carboplatin and paclitaxel. A 2-month increase in overall survival was observed (12.3 vs 10.3 months), p=0.003[54].

On the other hand there is another trial which evaluated the addition of bevacizumab to the combination of cisplatin and gemcitabine. Bevacizumab prolonged the progression-free survival by less than one month (6.7 vs 6.1 months). The overall survival was measured as a composite endpoint and no significant differences were found between the drug and placebo[55].

In further trials after the approval, no differences between bevacizumab and placebo with regard to overall survival were found[56,57,58,59]. In one of them[56], a paradox was observed in that the use of bevacizumab at low doses (7.5 mg/kg) was associated with differences in favour of the drug but at higher doses (15 mg/g) the effect was similar to placebo. In another trial the primary endpoint was overall survival, but this was modified to progression-free survival. The reason given was that the follow-up period was not sufficient to find differences in overall survival between the two groups[58]. Given that, after 18 months of follow-up, the progression-free survival was similar in both groups (a reduction of 0.6 months in the bevacizumab, 6.7 vs 6.1 months), it is unlikely that bevacizumab will significantly improve overall survival.

Bevacizumab and renal carcinoma

Bevacizumab (Avastin®) in combination with interferon alfa-2a is indicated for first line treatment of patients with advanced and/or metastatic renal cell cancer. In the EMA report there are 3 trials that justify this indication. In one of them this agent was employed in addition to interferon[43]. The primary endpoint was overall survival and bevacizumab did not prove better than placebo. However, progression-free survival was increased in 4.8 months (10.2 vs 5.4 months)[43,60].

Another trial that compared bevacizumab to placebo evaluated the time to progression, with differences found in favour of the drug, although the EMA report does not specify the data. However, no differences between both groups in disease-free survival nor were data on overall survival provided.

Finally, there is a trial that studies the effects of adding erlotinib to bevacizumab, but no improvements in disease-free survival (primary endpoint) were found between groups.

None of these clinical trials published later have shown improvements in overall survival with the use of bevacizumab[61,62,63]. One trial with overall survival as the primary endpoint did not offer data with regard to this issue and was suspended beforehand, without complying with the "pre-specified criteria of stopping the trial based on differences in overall survival in both groups[64]".

Cetuximab and colorectal cancer

Cetuximab (Erbitux®) is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer:

Some cases of irregular approvals by the drug regulatory agencies have been observed

· in combination with irinotecan-based chemotherapy or FOLFOX 4,
· as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

In the EMA report there are 5 trials combining other antineoplastic agents and one trial in monotherapy. Of those trials with combined therapy, one showed an improvement in overall survival of 3.5 months (23.5 vs 20 months, $p<0.01$) in patients that showed wild-type KRAS gene. No differences were found in the mutant KRAS group. In the other two trials no benefit was shown with regard to overall survival in patients with the wild-type KRAS gene, and in the other two studies nor were there differences with respect to placebo. In these last two trials, no differentiated information on patients was offered regardless of whether the patients presented or not the KRAS gene[65].

In the published trials the results are contradictory. In those studies that evaluated the presence of the wild-type KRAS gene, two of them did not show significant differences in overall survival between cetuximab and placebo[66-67]. On the other hand, there are two trials in which the group of patients with the wild-type KRAS gene presented a statistically significant better response to cetuximab, although of modest magnitude. The overall survival increased by 3.3 months (23.5 vs 20 months)[68] and 4.7 months (9.5 vs 4.8 months)[69]. In this trial cetuximab was employed in monotherapy. In another trial, in which the presence of the KRAS gene was not determined, no differences in overall survival between cetuximab and placebo were observed[70].

Regulatory agencies and controversial approvals of indications

Erlotinib and metastatic pacreatic cancer

Erlotinib (Tarceva®) in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer. In July 2006

the EMA rejected the authorization of this indication considering that the drug's adverse effects did not compensate its limited efficacy. At the request of the manufacturer, the EMA celebrated an extraordinary meeting with a panel of different experts and finally approved the indication. Three of the four experts in this panel had important connections with the pharmaceutical company owner of erlotinib[71,72,73].

Bevacizumab and breast cancer

In December 2007 a placebo-controlled trial on the efficacy of bevacizumab in breast cancer was submitted to the FDA for drug approval. The primary endpoint was overall survival in which no differences were found Upon request of the pharmaceutical company and with the consent of the FDA, the primary endpoint was switched to progression-free survival in which differences in favour of bevacizumab were observed. The FDA approved the indication in breast cancer through the fast track procedure and the EMA acted in similar fashion.

Two additional trials were carried out to better define the assumed beneficial effects in this indication. However in the two cases no differences vs placebo were found in progression-free survival or in overall survival. The FDA withdrew the indication whereas the EMA only withdrew its indication in combined therapy with docetaxel, while maintaining its use in association with paclitaxel[74,75,76,77].

Panitumumab and colorectal cancer

Panitumumab (Vectibix®) is indicated for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

In the EMA report there are two open trials to justify the approved indication [78]. In one of them, the use of panitumumab in patients that had progressed on prior oxaliplatin and irinotecan, showed an increase of 2 months in progression-free survival (16 vs 8 weeks) in patients with wild-type KRAS gene[77,79]. Unfortunately no differences in overall survival were observed. The other trial also evaluated the efficacy of panitumumab in combination with oxiplatin, irinotecan and bevacimuzab, but in this case as first-line treatment. The trial was early stopped after an interim analysis that showed a lower progression-free survival in the panitumumab group (10.0 vs 11.4 months, panitumumab and placebo respectively). An increasing trend in mortality in the panitumumab group was also observed, although the differences were not significant (overall survival = 19.4 vs 24.5 months, panitumumab and placebo, respectively).

The authors who published this trial concluded that the addition of panitumumab increased the toxicity and reduced the period progression-free survival, and therefore did not recommend this indication in clinical practice[77,80]. The EMA underlined in its report that the risk/benefit balance of this drug would continue to be studied while at the same time it approved the indication.

However the indication has not been revised as to date, and two new indications have been approved which are the management of patients with wild-type KRAS metastatic colorectal cancer:
· in first-line in combination with FOLFOX.
· in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

The EMA points out in its report that "although the benefits are relatively small, panituzumab combined with chemotherapy, could benefit some patients and toxicity can be adequately managed"". When determining what patients could benefit from treatment, it simply affirms that "the committee decided that the prescribers are in a better position to judge based on the individual characteristics of the patients[81]".

The two indications are based on two clinical trials in patients with metastatic colorectal cancer with wild-type KRAS gene. In one of them, panituzumab was studied as add-on therapy to FOLFOX4 and increased the progression-free survival by 1.6 months (9.6 vs 8.0 months), though the overall survival was not increased[82]. In the other trial, the progression-free survival was increased by 2 months (5.9 vs 3.9 months)[83]. In this study nor was there an increase in overall survival with respect to placebo. Another two later studies showed that the drug had a similar effect to placebo with regard to overall survival[84,85].

Gefitinib and lung cancer

Gefitinib (Iressa®) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK. After a fast-track approval, four phase II trials were carried out. In one of them, no differences in survival vs placebo were observed. In another two trials, comparing gefitinib to docetaxel, non-inferiority could not be shown and the EMA experts did not rule out that docetaxel was better than gefitinib. The fourth trial had a cross-over design that could not offer reli-

able data on survival. Given the evidence, the FDA withdrew the indication of gefitinib[86], while the EMA still maintains it currently[87].

Safety

Biological drugs usually cause many adverse reactions, including neutropenia, thrombocytopenia, anaemia, anorexia, insomnia, headache, eye disorders, hemorrhage, gastric problems, transami-nase level increments, and skin related problems.

Some of these problems can be mortal, as in the case of multifocal leucoencephalopathy casued by rituximab[88,39]. For these reasons, the risk/benefit balance of the intervention should be adequately evaluated and adverse reactions properly notified to the pharmacovigilance center.

In table 2, other adverse effects relevant to these drugs discussed in this paper are described.

Economic factor

The economic impact of these drugs is very considerable. In Navarre, with a population of approximately 600,000 inhabitants, annual public expenditure on biotechnology agents in cancer comes to about 8 million euros. Over the last five years, the number of patients under treatment has increased four-fold (from 200 to approximately 800 annually). The cost per patient in the last three years has declined, probably and partly due to the reductions in prices of the drugs approved by the government (Table 3).

Final considerations

Since the decade of the 1980s biotechnology drugs have been under development in the cancer related field. These agents present new mechanisms of action with respect to chemotherapy employed up to now. This led to increased hopes that the pharmacological management of cancer would take an important step forward. Some of these drugs have shown a considerable advance and many patients are benefitting from them. This is the case of imatinib in chronic myeloid leukaemia cetuximab in locally advanced scamous cancer of the head and neck, trastuzumab in cases of metastatic breast cancer or rituximab in patients with non-Hodgkin lymphoma.

However, all that glitters is not gold. The majority of the drugs on the market have been approved through a fast track process based on the results

Some drugs have shown a significant improvement, but many present questionable efficacy with regard to overall survival

on surrogate endpoints (progression-free survival, overall response, etc.) which in many occasions, do not correlate with the increase in the overall survival. It would be justified to employ these variables in cases of clinical trials which last many years, normally due to the slow evolution of a tumor, and always and whenever there is an unequivocal correlation with overall survival. Unfortunately, the reality is that these agents are being employed without these two conditions. Habitually, these factors are used to justify their approval in cancer without the need of demonstrating any clinically objective advantage.

Besides the dubious capacity to estimate overall survival of the surrogate endpoints, it should be mentioned that their measurement is in part subjective. In fact, in the trials in which the results obtained by researchers are contrasted with an evaluation by a panel of experts, there are habitually notable differences. This raises further doubts on the exactitude and veracity of the findings based on the results on surrogate endpoints, especially when its magnitude is small. Evidently, this is not the case with hard endpoints such as overall survival.

Along with the use of surrogate endpoints, the regulatory agencies are approving many cancer related drugs based on the studies carried out with very few patients, of short duration, in some cases open phase II trials, and with questionable results. It should be no surprise that in some cases, the results of these pivotal trials employed to obtain approval of a drug cannot be confirmed by further studies or the results are worse than those described in the pivotal trials. For instance, this is the case of sorafenib in renal cancer or bevacizumab in colorectal cancer.

A debate should be carried out regarding whether a drug which prolongs life for one or two months should be approved or financed publicly. But it is even more unsettling to confirm that many drugs that do not improve overall survival are approved by regulatory agencies and place an authentic

Table 2. Main adverse effects of biotechnology drugs.

DRUG	MAIN ADVERSE EFFECTS
Alemtuzumab[38]	Severe or fatal infections. Latent tuberculosis must be ruled out and prophylaxis against opportunistic agents should be considered. Severe infusion-related reactions, myelosupression and hematologic toxicity. If ischaemic heart disease, infusion-related hypotension, myocardial infarction and cardiac arrest may occur.
Bevacizumab[40]	Intestinal perforation, fistula and intra-abdominal abscess. Do not start treatment within 28 days after surgery. Contraindicated in colorectal cancer patients and in cases of haemorrhage or hemoptisis.
Cetuximab[7]	Dyspnea (25%) in advance colorectal cancer, hypersensitivity (1-10%), skin and subcutaneous reactions (>10%).
Dasatinib[15]	Cardiovascular events (heart failure, left ventricular dysfunction, pulmonary hypertension, myocardial infarction and diastolic dysfunction).
Erlotinib[19]	Intestinal perforation (avoid concomitant use of NSAIDs or corticosteroids), skin and ophthalmic reactions (ulcers or corneal perforation).
Gefitinib[86]	Dyspnea (15%), lower respiratory tract infections (10%), neurotoxicity (10%), rash or acne (50%).
Imatinib[5]	Epistaxis, dyspnea, raised serum transaminases, dermatitis, oedema, exanthematous eruptions, muscular spasm and cramps.
Lapatinib[28]	Hyperbilirubinemia and hepatotoxicity (1-10%), left ventricular ejection fraction decrease (2%), asymptomatic in most patients and resolves spontaneously after drug withdrawal in 60% of cases. Skin reactions: exanthematous eruptions (30%), hand-foot syndrome (50%).
Nilotinib[20]	Cardiovascular events (1-10%): palpitations, QT interval prolongation, hypertension and flushing; less frequently (0,1-1%): heart failure, angina, atrial fibrillation, pericardial effusion, coronary disease, cardiomegaly, cardiac murmur, bradycardia, hypertensive crisis and hematoma; skin reactions (>10%).
Panitumumab[77]	Dyspnea and cough (>10%), allergy and dermatology reactions (>10%).
Rituximab[15]	Infusion-related reactions, cardiovascular events (1-10%): myocardial infarction, arrythmia, atrial fibrillation, tachycardia; toxic epidermal necrolysis, intestinal perforation, haematological disorders, hepatitis B reactivation, tumoral lysis syndrome, progressive multifocal leukoencephalopathy, bronchiolitis obliterans, pneumonitis, other infections.
Sorafenib[31]	Hand-foot syndrome (20%), exanthematous eruptions (30%), hypertension (10%).
Sunitinib[36]	Hypertension (15%), left ventricular ejection fraction decrease of 20%. If heart failure symptoms present, stop sunitinib treatment; if no symptoms but left ventricular ejection fraction <50% and >20% below baseline, withdraw treatment or reduce dose, QT interval prolongation, bradycardia or arrhythmia.
Temsirolimus[39]	Dyspnea (30%), lumbalgia, muscular pain (>10%), angina-like chest pain (>10%), hypertension, thromboembolism (1-10%), hyperglycemia, dyslipidemia, hypokalemia, infections (>10%), raised serum transaminases (1-10%).
Trastuzumab[12]	Osteomuscular pain or myalgia (>10%), exanthematous eruptions (>10%), cardiovascular events (vasodilation, supraventricular tachycardia, hypotension, heart failure symptoms) (1-10%), oedema (1-10%), hepatotoxicity.

Table 3. Expenditure on cancer related biotechnology drugs in Navarre.

	2007	2008	2009	2010	2011*
Trastuzumab	1,612,990	1,819,577	1,377,245	1,573,518	1,596,276
Bevacizumab	407,762	998,149	1,460,158	1,764,368	1,422,398
Cetuximab	329,987	697,972	816,967	753,370	1,191,709
Rituximab	514,761	643,045	909,982	1,009,533	934,390
Imatinib	30,789	470,347	930,834	887,303	800,800
Sunitinib	11,190	355,376	537,030	876,796	785,534
Sorafenib	47,996	44,304	70,148	69,222	318,213
Erlotinib	14,089	168,760	390,544	409,969	287,539
Milotinib	0	37,526	86,309	231,158	203,002
Gefitinib	0	0	0	65,252	70,559
Panitumumab	0	16,642	31,619	59,576	66,532
Lapatinib	0	23,664	164,560	122,787	57,484
Temsirolimus	0	30,374	39,865	23,049	33,565
Alemtuzumab	3,662	0	44,390	5,947	11,804
Dasatinib	7,355	99,293	15,010	18,763	4,614
Total	2,980,551	5,405,028	6,874,662	7,870,612	7,784,418
Nº treated patients	**215**	**415**	**575**	**675**	**809**
Mean cost per patient	**13,863**	**13,024**	**11,956**	**11,660**	**9,618**

(*) Data January-October extrapolated to the full year.

burden on public expenditure of health systems and on private patients.

In addition to this there is the irregular behaviour of the main regulatory agencies, like the EMA and FDA, which have approved some drugs of known inefficacy, considering the results in clinically irrelevant endpoints, or when the risk/benefit balance does not recommend the use of the drug in question.

It is true that cancer patients are special, normally bear a feeling their lives are under threat, and that our society bears a special sensitivity to cancer. However we should not lose sight of our common sense and scientific rigor. Perhaps we should remember a recent event in medical oncology. In the mid 1990s intensive chemotherapy with bone marrow transplant was popular in advanced breast cancer instead of conventional treatment. With time it was discontinued when a 3-5% increase in mortality related to treatment was observed, elevated morbidity (severe infections and mucositis) was seen, the efficacy in clinical practice was inexistent, and management costs raised very high[89]. Perhaps the time has come to demand more scientific rigor in the approval and use of cancer related drugs. Moreover, sooner or later, the question will be raised about up to where can we or do we want to bear with public funds the costs of these drugs many of which do not offer clear advantages in terms of overall survival.

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Conclusions

Some biotechnology drugs have shown to be useful in the management of cancer. However, the efficacy of the majority of them is questionable, they present considerable adverse effects and are very expensive.

It is convenient to act with greater scientific rigor when approving or withdrawing the authorization of these drugs.

The public health system should address the selective funding of these drugs.

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