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Medicines in exceptional circumstances for solid tumours: focusing on evidence, effectiveness, and toxicity profiles

Medicamentos en situaciones especiales para tumores sólidos: profundizando en la evidencia y los perfiles de efectividad y toxicidad

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Abstract

Objective: To analyse the applications for drugs in special situations (compassionate use, off-label use and foreign drugs) for solid tumours, and to assess the level of evidence supporting these applications, as well as the effectiveness and safety of most frequent drugs.

Method: We performed a cross-sectional study of all applications for drugs in special situations during 2018 and 2019 in a representative third-level centre. We collected data about generic names of drugs, clinical indications, and level of evidence provided on the application form. Furthermore, tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours version 1.1., Progression Free Survival and Overall Survival. Safety was evaluated with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Results: 2,273 drugs in special situations were approved between January 2018 and December 2019. In 431 cases (19%), they were used to treat solid tumours. Out of 431, 291 (67.5%) applications were off-label drugs, 76 (18%) foreign drugs, and 64 (15%) were compassionate use of drugs. Most of them were supported by phase 3 (47%) or phase 2 (33%)

KEYWORDS
Evidence-based medicine; Clinical trials; Compassionate use; Expanded access; Investigational drugs; Off-label use.

Resumen

Objetivo: Analizar las solicitudes de medicamentos en situaciones especiales (uso compasivo, uso fuera de indicación y medicamentos extranjeros) para tumores sólidos, y evaluar el nivel de evidencia que avala dichas solicitudes, así como la efectividad y seguridad de los medicamentos más frecuentes.

Método: Estudio transversal que incluyó las solicitudes de medicamentos en situaciones especiales durante el período 2018-2019 en un centro representativo español de tercer nivel. Se recogieron datos sobre principios activos, indicaciones clínicas y nivel de evidencia aportado en la solicitud. Asimismo, la respuesta tumoral fue evaluada mediante criterios Response Evaluation Criteria in Solid Tumours versión 1.1, supervivencia libre de progresión y supervivencia global. La seguridad fue evaluada con la versión 5.0 de los criterios de toxicidad Common Terminology Criteria for Adverse Events del National Cancer Institute de Estados Unidos.

Resultados: Un total de 2.273 medicamentos en situaciones especiales fueron aprobados entre enero de 2018 y diciembre de 2019. El 19% (431) se aprobaron para el tratamiento de tumores sólidos. De estos 431, 291 (67,5%) solicitudes fueron de medicamentos fuera de indicación, 76 (18%) extranjeros y 64 (15%) en uso compasivo. La mayoría son

PALABRAS CLAVE
Medicina basada en la evidencia; Ensayos clínicos; Uso compasivo; Acceso ampliado; Medicamentos en investigación; Uso fuera de indicación.

clinical trials. The majority of adverse effects were grade 1 and only in 6/67 cases the treatment was discontinued due to toxicity.
Conclusions: A significant number of drugs in special situations are prescribed to Oncology patients. The majority of applications of these drugs was supported by clinical trials. The real-life experience showed an effectiveness and tolerance profile similar to those described in randomised clinical trials.

avaladas por estudios clínicos aleatorizados en fase III (47%) o fase II (33%). La mayor parte de los efectos adversos fueron de grado 1 y solo en 6/67 casos el tratamiento fue interrumpido por toxicidad.
Conclusiones: Un porcentaje importante de medicamentos en usos especiales se prescriben a pacientes oncológicos. La mayoría de las solicitudes fueron avaladas por algún estudio clínico aleatorizado. La experiencia en vida real mostró un perfil de efectividad y tolerancia similar al descrito en los estudios clínicos aleatorizados.

Introduction

Delay in the approval and marketing of new pharmaceuticals, especially in the field of Medical Oncology, can imply that promising drugs are not authorised, in spite of existing evidence base supporting their use. As a consequence, drugs in special situations have emerged as a treatment option that allows the use of an unauthorised medicine[1]. The level of evidence supporting off-label drug use in clinical practice has been scarcely addressed in the literature[2].

Over the years, compassionate use has evolved to become a very complex issue involving pharmaceutical companies, regulatory agencies, physicians, patients and patient advocacy groups[3].

The use of drugs in exceptional circumstances refers to the use of non-authorised medicines or the use of medicines outside their authorised conditions, and includes:

1. Off-label use: the use of an authorised medicinal product for an indication different from those provided for product characteristics.
2. Compassionate use: the use of investigational drugs (unauthorised) in patients with no satisfactory authorised therapies and who cannot enter RCTs.
3. Foreign drugs: the use of medicines unauthorised in Spain but authorised in other countries[4].

The Spanish legislation limits the use of each of these criteria to those exceptional circumstances in which there is no other commercial therapeutic alternative. The process of drugs in exceptional circumstances' authorisation in case of unauthorised drugs in our country (compassionate use or foreign drugs) has multiple steps (in sequence): a) the informed consent of the patient; b) the request of a specialist physician; c) the agreement of the Medical Chief Director of the healthcare centre and, finally d) authorisation by the Spanish Agency of Medicines and Medical Devices[4]. In some cases, the agreement of the promoter or pharmaceutical company is also required. In the case of the off-label use, authorisation from the Spanish Agency is not required. The physician must adequately justify in the clinical history the need for the use of the medicine and inform the patient of the possible benefits and potential risks.

Article 6 of Directive 2001/83/EC1 requires that medicinal products are authorised before they are marketed in the European Community[5]. This article formulates only two general requirements for compassionate use: 1) a chronically or seriously debilitating disease, or a life threatening disease of patients who cannot be treated satisfactorily with an authorised medicinal product, and 2) the medicinal product must be either the subject of an application for a centralized marketing authorisation or be undergoing clinical trials[3]. Compassionate use (CU) programmes are coordinated by Member States, which set their own rules and procedures[6].

A literature review explored compassionate use in 28 EU member states, concluding that compassionate use program (CUP) was present in 20 EU member states (71%). Of 28 EU states, 18 had nationalized regulations and processes were well-defined[7].

Patients should always be considered for inclusion in randomized clinical trials (RCTs) before being offered compassionate use programmes. RCTs are practically the best means of obtaining reliable and interpretable efficacy and safety data for a medicinal product[5].

In 2014, the number of requests for expanded access to investigational new drugs received by the Food and Drug Administration increased by two-fold compared to those received in 2005. Anti-cancer drugs represented approximately a quarter of the applications. Overall, 99.7% of the submitted requests for expanded access were accepted[8].

The aims of this study were:

- To analyse the applications for drugs in special situations for solid tumours in a representative Spanish third-level centre, describing the authorised drugs (generic names) and their indications.
- To assess the level of evidence supporting these applications.
- To evaluate effectiveness and safety of most frequent drugs used in special situations.

Methods

Study design

We conducted a cross-sectional study of all applications for drugs in special situations during 2018 and 2019 in a representative third-level hospital. All drugs in special situations were identified and of these, the drugs used for solid tumours were selected to perform this study.

Variables

We collected data about generic names of drugs, indications, and level of evidence provided (according to the hierarchy of study types and its correlation to levels of clinical evidence established by National Health and Medical Research Council [NHMRC] and National Institute for Clinical Excellence [NICE]: animal and laboratory studies, case report or case series, observational studies, and RCTs —divided into three phases—).

The baseline characteristics of patients, such as age and Eastern Cooperative Oncology Group (ECOG) performance score, were analysed. Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, Progression Free Survival (PFS) and Overall Survival (OS). Safety was evaluated with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. We also collected data about time to adverse effect and need for change of treatment. Finally, we discussed and compared our real-world experience data with those published from RCTs.

Data collection and drug approvals

Data were obtained from the database of drugs in special situations recorded by the drug information centre of the Hospital Pharmacy department (software PKusos® https://www.pksiam.com/service/pkusos/)[9].

Before authorizing the drug used in special situation, a multidisciplinary team evaluates the available evidence on its use in this special situation. Each submitted application was considered on a case-by-case basis. An ad hoc Hospital Committee evaluated whether each request met the criteria to be used as a medicine in exceptional circumstances. Those drugs evaluated by the Hospital Committee with a positive assessment of the submitted application for antineoplastic drugs in a special use situation were collected.

Statistical analysis

Statistical analysis was performed using Stata (developed by StataCorp), and the MS Excel (Microsoft) was used to create figures and charts. Frequencies and percentages were used for categorical variables and means (standard deviations, SD) or medians (interquartile ranges, IQR) for continuous variables, depending on the distribution of the variable. Survival was analysed using Kaplan-Meier curves.

Table 1. Frequency of clinical indications (types of tumours) and level of evidence of medicines in special circumstances provided at the moment of application

Type of tumour	n (%)
Hepatocellular carcinoma	58 (13.4%)
Lung cancer	57 (13.2%)
Breast cancer	52 (12.0%)
Gastric cancer	33 (7.6%)
Neuroendocrine tumour	26 (6.0%)
Squamous cell carcinoma	25 (5.8%)
Sarcoma	20 (4.6%)
Endometrial adenocarcinoma	17 (3.9%)
Melanoma	14 (3.2%)
Osteosarcoma	14 (3.2%)
Cervical cancer	12 (2.7%)
Glioblastoma	12 (2.7%)
Pancreatic adenocarcinoma	10 (2.3%)
CRC	9 (2.0%)
CRPC	9 (2.0%)
Ovarian cancer	7 (1.6%)
Urothelial carcinoma	4 (0.9%)
RCC	3 (0.6%)
Others	49 (11.3%)
Study type	**n (%)**
Phase 1 trial	12 (3.2%)
Phase 2 trial	120 (32.8%)
Phase 3 trial	172 (47.1%)
Observational study	11 (3.0%)
Case series	31 (8.5%)
Experimental/animal research	2 (0.5%)
Case report	17 (4.6%)

CRC: colorectal cancer; CRPC: castration-resistant prostate cancer; RCC: renal cell carcinoma.

Results

Overall, 2,273 drugs in special situations were approved between January 2018 and December 2019 (99.5% of total applications). In 431 (19%) applications, the diagnosis was a solid tumour.

Regarding the frequency distribution of departments which requested for drugs in special circumstances, the most common clinical department was ophthalmology with 440 applications (19.3%), followed by oncology —431 (18.9%)— and hematology —289 (12.7%).

Table 1 shows the clinical indications of drugs in special situations for solid tumours and level of evidence provided at the moment of application.

Hepatocellular carcinoma (13.4%), lung cancer (13.2%) and breast cancer (12%) were the most treated pathologies using drugs in special situations. We obtained information about the level of evidence provided at the moment of application in 365 cases (84.9%). The majority of drugs in special situations were supported by phase 3 (47%) o phase 2 (33%) trials (Table 1).

Out of 431, 291 (67.5%) applications for solid tumours were off-label drugs, 76 (18%) foreign drugs, and 64 (15%) were compassionate use of drugs. The table 2 summarizes data about drugs in special situations for solid tumours.

Figure 1 shows the most frequent drugs (generic names) in special situations for solid tumours during 2018-2019. Ethiodol, oxaliplatin and durvalumab were the most commonly prescribed foreign, off-label use and compassionate drugs, respectively.

Table 3 contains the data regarding effectiveness and safety of most commonly prescribed drugs in special situations during the study period. Some missing values were detected (follow-up in other centres, deaths before the CT examination, etc.). Real-world RECIST–based complete or partial responses were found in 28.6% of patients treated with oxaliplatin for gastric cancer, 40% of patients diagnosed with squamous cell carcinoma treated with paclitaxel, 7.7% of palbociclib uses in breast cancer patients, and in 33.33% of patients with cervical cancer who were treated with pembrolizumab. The majority of toxicities were grade 1 according to CTCAE 5.0 and only in 6/67 cases the treatment was discontinued due to adverse effects.

Figure 1. *Frequency of drugs in exceptional circumstances approved for solid tumours.*

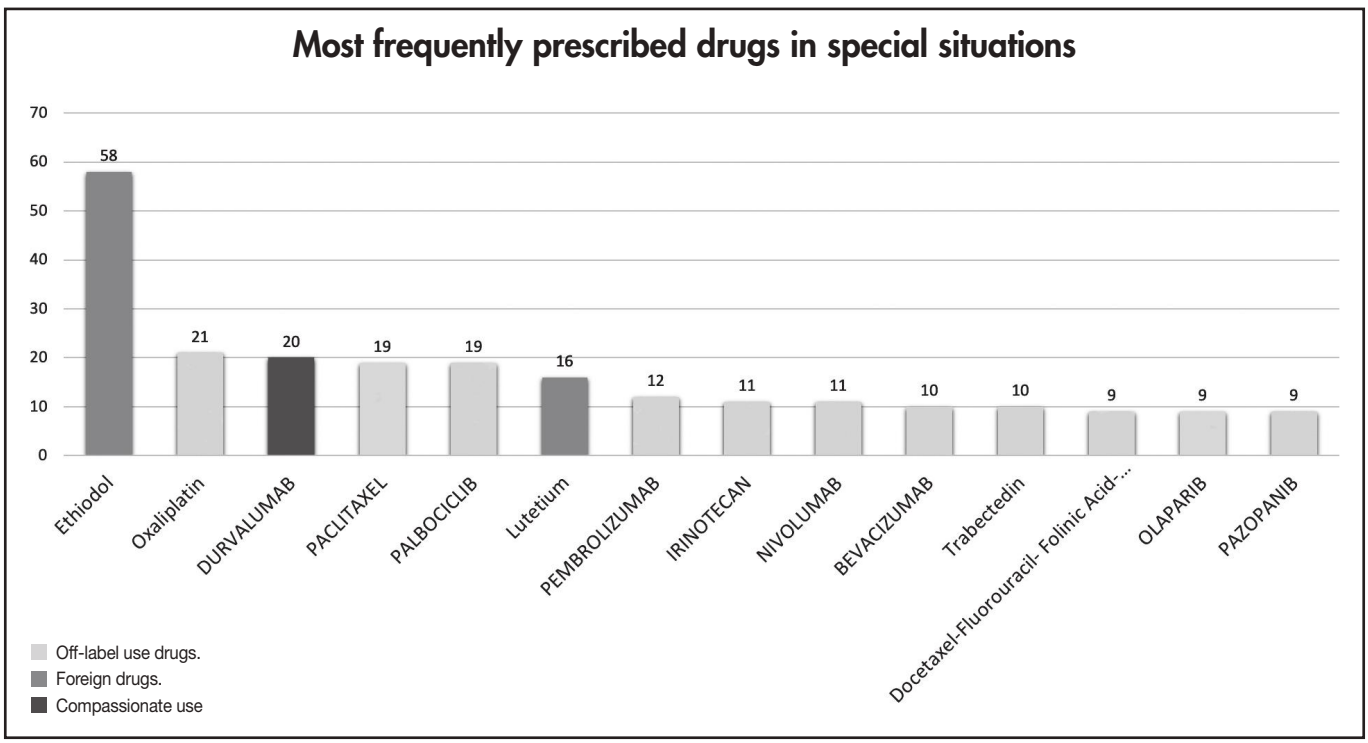

Table 2. Off-label use (OLU), compassionate use (CU) and foreign drugs (FD) approved for solid tumours between 2018 and 2019

Drug (generic name)	Number of applications	Type	Use	Other uses	Evidence provided	Department
Off-label use (OLU) drugs						
Oxaliplatin	21	OLU	Gastric cancer (n = 20)*		Phase 3 trial	Medical Oncology
Paclitaxel	19	OLU	Head and neck squamous cell carcinoma (n = 6)*	Angiosarcoma (n = 5)* SCLC (n = 4)* Melanoma (n = 2)*	– Head and neck squamous cell carcinoma: Phase 2 trial – Angiosarcoma: Phase 2 trial – Melanona: Phase 3 trial	Medical Oncology
Palbociclib	19	OLU	Breast cancer (n = 17)*	Liposarcoma Glioblastoma	– Breast cancer: Case series – Liposarcoma: Phase 2 trial	Medical Oncology
Pembrolizumab	12	OLU	Cervical cancer (n = 4)*	Cavum lymphoepithelioma Gallbladder carcinoma	– Cervical cancer: Phase 2 trial – Cavum lymphoepithelioma: Phase 1 trial	Medical Oncology
Irinotecan	11	OLU	Lung cancer (SCLC) (n = 6)*	Glioblastoma. (n = 3)* Undifferentiated sarcoma	SCLC: Phase 3 trial	Medical Oncology
Nivolumab	11	OLU	Melanoma	Colorectal cancer	– Melanoma: Phase 3 trial – CCR: Phase 2 trial	Medical Oncology
Bevacizumab	10	OLU	Endometrial adenocarcinoma	Glioblastoma. Astrocytoma	Phase 2 trial	Medical Oncology
Trabectedin (ET-743)	10	OLU	Sarcoma	Fibrous tumour	– Sarcoma: Phase 3 trial – Fibrous tumour: Observational study	Medical Oncology
Docetaxel-Fluorouracil- Folinic Acid-Oxaliplatin	9	OLU	Gastric cancer	Esophageal adenocarcinoma Pancreatic adenocarcinoma	Phase 2 trial and phase 3 trial	Medical Oncology
Olaparib	9	OLU	Breast cancer	Ovarian cancer Pancreatic adenocarcinoma	– Breast cancer: Phase 3 trial – Pancreatic adenocarcinoma: Phase 2 trial	Medical Oncology
Pazopanib	9	OLU	Chondrosarcoma	Liposarcoma GIST	– Chondrosarcoma: Case report – Liposarcoma: Phase 2 trial	Medical Oncology
Non-pegylated liposomal doxorubicin	8	OLU	Breast cancer (Adjuvant chemotherapy)		Phase 2 trial and phase 3 trial	Medical Oncology
Capecitabine	7	OLU	Neuroendocrine tumour	Adrenocortical carcinoma Cholangiocarcinoma	– NET: Case series – Adrenocortical carcinoma: Phase 2 trial	Medical Oncology
Fotemustine	7	OLU	Glioblastoma		Phase 2 trial	Medical Oncology
Trastuzumab emtansine	7	OLU	Breast cancer		Phase 3 trial	Medical Oncology
Cisplatin + Doxorubicin	6	OLU	Peritoneal carcinomatosis arising from ovarian or colorectal cancer		Protocolized use	Medical Oncology

Table 2 *(cont.).* Off-label use (OLU), compassionate use (CU) and foreign drugs (FD) approved for solid tumours between 2018 and 2019

Drug (generic name)	Number of applications	Type	Use	Other uses	Evidence provided	Department
Off-label use (OLU) drugs						
Everolimus	6	OLU	Endometrial adenocarcinoma		Phase 2 trial	Medical Oncology
Ifosfamide	6	OLU	Osteosarcoma	Malignant peripheral nerve sheath tumour	Phase 2 trial	Medical Oncology
Imatinib	6	OLU	Lung cancer (KIT mutation)	Desmoid tumour	Lung cancer: Case report	Medical Oncology
Docetaxel	5	OLU	Sarcoma	Endometrial adenocarcinoma	Phase 2 trial	Medical Oncology
Enzalutamide	5	OLU	CRPC	Breast cancer	Breast cancer: Phase 2 trial	Medical Oncology Radiation Oncology
Albumin-bound pablitaxcel	5	OLU	Cholangiocarcinoma	Breast cancer	Cholangiocarcinoma: Phase 2 trial	Medical Oncology
Procarbazine + lomustine + vincristine	5	OLU	Glioblastoma	Oligodendroglioma	Phase 2 trial and phase 3 trial	Medical Oncology
Carboplatin	4	OLU	CRPC	Germ cell tumour. Peripheral nerve tumour	– CRPC: Phase 2 trial – Germ cell tumour: Phase 2 trial	Medical Oncology
Encorafenib	4	OLU	Colorectal cancer		Phase 3 trial	Medical Oncology
Gemcitabine + Capecitabine	4	OLU	Pancreatic adenocarcinoma		Phase 3 trial	Medical Oncology
Gemcitabine + Docetaxel	4	OLU	Osteosarcoma		Observational study	Medical Oncology
Sorafenib	4	OLU	Osteosarcoma		Phase 2 trial	Medical Oncology
Capecitabine + Temozolamide	3	OLU	Neuroendocrine tumour	Colorectal cancer	Case series	Medical Oncology
Cetuximab	3	OLU	Cutaneous squamous-cell carcinoma		Phase 2 trial and observational study	Medical Oncology
Cisplatin	3	OLU	Anaplastic astrocytoma	Chondrosarcoma	Astrocytoma: Phase 2 trial	Medical Oncology
Gemcitabine + Dacarbazine	3	OLU	Soft-tissue sarcoma		Phase 2 trial	Medical Oncology
Irinotecan + Temozolomide	3	OLU	Rhabdomyosarcoma	Ewing's sarcoma	Observational study	Medical Oncology
Pertuzumab	3	OLU	Breast cancer		Phase 3 trial	Medical Oncology
Temozolomide	3	OLU	Malignant mesenchymal tumour	Ewing's sarcoma	Observational study and phase 1 trial	Medical Oncology
Trifluridine/ Tipiracil	3	OLU	Gastric cancer		Phase 2 trial and phase 3 trial	Medical Oncology
Dacarbazine	2	OLU	Soft-tissue sarcoma		Phase 2 trial and phase 3 trial	Medical Oncology
Gemcitabine	2	OLU	Angiosarcoma		Case series	Medical Oncology

Table 2 *(cont.).* Off-label use (OLU), compassionate use (CU) and foreign drugs (FD) approved for solid tumours between 2018 and 2019

Drug (generic name)	Number of applications	Type	Use	Other uses	Evidence provided	Department
Off-label use (OLU) drugs						
Ipilimumab	2	OLU	Renal cell carcinoma	Colorectal cancer	– RCC: Phase 3 trial – CRC: Phase 2 trial	Medical Oncology
Mitomycin-C	2	OLU	Colorectal cancer		Phase 3 trial and observational study	Medical Oncology
Sulindac	2	OLU	Musculoskeletal fibromatosis		Observational study	Medical Oncology
Topotecan	2	OLU	Ewing's sarcoma	Rhabdomyosarcoma	Phase 2 trial	Medical Oncology
Trametinib	2	OLU	Melanoma	Ovarian cancer	– Melanoma: Phase 3 trial – Ovarian cancer: Phase 2/3 trial	Medical Oncology
Trastuzumab	2	OLU	Colorectal cancer	Uterine serous carcinoma	– CRC: Phase 2 trial – Uterine serous carcinoma: Phase 2 trial	Medical Oncology
Abiraterone	1	OLU	Salivary gland carcinoma		Case series	Medical Oncology
Doxorubicin (Adriamycin)	1	OLU	Solitary fibrous tumour		Experimental (Preclinical study)	Medical Oncology
Alectinib	1	OLU	Lung cancer (NSCLC)		Phase 3 trial	Medical Oncology
Carboplatin + Vinorelbine	1	OLU	Sarcoma		Case report	Medical Oncology
Cyclophosphamide	2	OLU	Ewing's sarcoma	Chondrosarcoma	Phase 2 trial	Medical Oncology
Crizotinib	1	OLU	Lung cancer		Experimental (Preclinical study)	Medical Oncology
Dabrafenib	1	OLU	Melanoma		Phase 3 trial	Medical Oncology
Dexrazoxane	1	OLU	Sarcoma		Phase 2 trial	Medical Oncology
Pegylated liposomal doxorubicin	1	OLU	Desmoid tumour		Observational study	Medical Oncology
Erlotinib	1	OLU	Chordoma		Case series	Medical Oncology
Etoposide	1	OLU	Pilomatrix carcinoma		Case report	Medical Oncology
Lenvatinib	1	OLU	Endometrial adenocarcinoma		Phase 2 trial	Medical Oncology
Lomustine + Cisplatin + Vincristine	1	OLU	Medulloblastoma		Phase 3 trial	Medical Oncology
Nivolumab + Ipilimumab	1	OLU	Colorectal cancer		Phase 2 trial	Medical Oncology
Pemetrexed	1	OLU	Urothelial carcinoma		Phase 2 trial	Medical Oncology
Sirolimus	1	OLU	Chondrosarcoma		Case series	Medical Oncology
Tivozanib	1	OLU	Renal cell carcinoma		Phase 3 trial	Medical Oncology
Vinorelbine	1	OLU	Rhabdomyosarcoma		Phase 3 trial	Medical Oncology

Table 2 *(cont.).* Off-label use (OLU), compassionate use (CU) and foreign drugs (FD) approved for solid tumours between 2018 and 2019

Drug (generic name)	Number of applications	Type	Use	Other uses	Evidence provided	Department
Compassionate use (CU) drugs						
Durvalumab	20	CU	Lung cancer (NSCLC) (n = 18)*		Phase 3 trial	Medical Oncology
Nanoliposomal irinotecan (nal-IRI)	6	CU	Pancreatic adenocarcinoma (n = 6)*		Phase 3 trial	Medical Oncology
Niraparib	6	CU	Ovarian serous carcinoma (n = 6)*		Phase 3 trial	Medical Oncology
Lorlatinib	5	CU	Lung cancer (NSCLC) (n = 5)*		Phase 2 trial	Medical Oncology
Lurbinectedin	4	CU	Lung cancer (SCLC) (n = 4)*		Phase 2 trial	Medical Oncology
Abemaciclib	3	CU	Breast cancer		Phase 2 trial	Medical Oncology
Atezolizumab	3	CU	Urothelial carcinoma		Phase 2 trial and phase 3 trial	Medical Oncology
Brigatinib	3	CU	Lung cancer (NSCLC)		Phase 1 trial and preclinical study	Medical Oncology
Capmatinib	3	CU	Lung cancer (NSCLC)		Phase 2 trial	Medical Oncology
Cemiplimab	3	CU	Cutaneous squamous-cell carcinoma		Phase 1 trial	Medical Oncology, Dermatology
Rovalpituzumab tesirine	2	CU	Lung cancer (SCLC)		Phase 1 trial	Medical Oncology
Neratinib	1	CU	Ovarian serous carcinoma		Observational study	Medical Oncology
Osimertinib	1	CU	Lung cancer (NSCLC)		Phase 3 trial	Medical Oncology
Sapanisertib	1	CU	Breast cancer		–	Medical Oncology
SFX-01	1	CU	Breast cancer		–	Medical Oncology
Talazoparib	1	CU	Breast cancer BRCA+		–	Medical Oncology
Tazemetostat	1	CU	Sarcoma		Phase 1 trial	Medical Oncology
Foreign drugs (FD)						
Ethiodol	58	FD	Hepatocellular carcinoma (n = 58)*		Protocolized use	Radiology
Lutetium	16	FD	Neuroendocrine tumour (n = 9)*		Phase 3 trial	Medical Oncology
Actinomycin D	2	FD	Rhabdomyosarcoma (n = 2)*		Phase 3 trial	Medical Oncology

The asterisk (*) indicates that their effectiveness and toxicity profiles were analysed (see Table 3). Some missing values were detected (follow-up in other centres, deaths before the CT evaluation…).

CRC: colorectal cancer; CRPC: castration-resistant prostate cancer; GIST: gastrointestinal stromal tumour; NET: neuroendocrine tumour; NSCLC: non-small-cell lung carcinoma; RCC: renal cell carcinoma; SCLC: small cell lung cancer.

Table 3. Real-life experience on effectiveness and safety of the most frequently prescribed drugs in special situations.

Drug name	Use	Age	ECOG	Treatment duration, days	Effectiveness			Adverse effects					Successive chemotherapy lines
					Efficacy according to RECIST criteria	PFS	Overall survival	Rate of adverse effects	Toxicity according to CTCAE 5.0	Type of adverse effects	Time to adverse effect, days	Change of treatment due to adverse effects	
Off-label use (OLU) drugs													
Oxaliplatin	Gastric cancer (n = 20)	69.4 (SD 12.3)	0: 6 (33.3%) 1: 12 (66. 7%)	109.2 (SD 66.1)	CR: 0 PR: 4 (28.6%) SD: 5 (35.7%) PD: 5 (35.7%)	At 12 mo, 70%	P50: 10.5 24 mo: 25%	14 (70.0%)	G1: 1 (50.0%) G2: 1 (50.0%) G3: 0	Neutropenia: 1 (7.1%) Thrombocytopenia: 1 (7.1%) Loss of appetite: 5 (71.4%) Nausea and vomiting: 1 (7.1%) Fatigue: 11 (78.5%) Peripheral neuropathy: 1 (7.1%) Diarrhea: 1 (7.1%)	87.9 (SD 91.5)	1 (7.1%)	4 (20.0%)
Paclitaxel	Angiosarcoma of soft tissue (n = 5)	65.8 (SD 11.6)	0: 1 (33.3%) 1: 1 (33.3%) 2: 1 (33.3%)	154.8 (SD 138.8)	CR: 0 PR: 0 SD: 1 (25.0%) PD: 3 (75.0%)	At 12 mo, 30%	P50: 5.4 24 mo: 20%	2 (40.0%)	G1: 1 (50,0%) G2: 1 (50,0%) G3: 0	Neutropenia and thrombocytopenia: 1 (50.0%) Peripheral neuropathy: 1 (50.0%)	130.5 (SD 125.2)	1 (50.0%)	1 (20.0%)
	SCLC (n = 4)	72 (SD 8.2)	0: 2 (50%) 1: 2 (50%)	72.33 (SD 90.0)	CR: 0 PR: 0 SD: 0 PD: 1 (100%)	At 6 mo, 0%	P50: 1.9 24 mo: 0%	2 (50.0%)	G1: 2 (100%) G2: 0 G3: 0	Fatigue: 2 (100%)	49 (SD 49.5)	0	0
	Melanoma (n = 2)	62 (SD 21.2)	0: 2 (100%)	–	–	–	P50: 1.5 12 mo: 0%	0	–	–	–	–	1 (50.0%)
	Squamous cell carcinoma (n = 6)	65.5 (SD 10.0)	0: 3 (50%) 1: 3 (50%)	155.2 (SD 84.0)	CR: 1 (20.0%) PR: 1 (20.0%) SD: 0 PD: 3 (60.0%)	At 12 mo, 33.3%	P50: 9.8 24 mo: 33.3%	5 (83.3%)	G1: 3 (60%) G2: 2 (40%) G3: 0	Neutropenia: 1 (20%) Rash: 2 (40%) Peripheral neuropathy: 2 (40%)	120.2 (SD 87.3)	1 (20.0%)	4 (66. 7%)
Palbociclib	Breast cancer (n = 17)	60.5 (SD 12.3)	0: 12 (70.6%) 1: 4 (23.5%) 2: 1 (5.9%)	190.4 (SD 134.6)	CR: 0 PR: 1 (7.7%) SD: 0 PD: 12 (92.3%)	At 12 mo, 21.2%	P50: 17.3 24 mo: 29.4%	13 (76.5%)	G1: 9 (69.2%) G2: 3 (23.1%) G3: 1 (7.7%)	Rash: 1 (7.7%) Neutropenia: 1 (7.7%) Loss of appetite: 5 (71.4%) Nausea and vomiting: 1 (7.7%) Fatigue: 5 (38.5%) Peripheral neuropathy: 4 (30.8%) Constipation: 1 (7.7%) Sense of abdominal fullness: 1 (7.7%)	155.1 (SD 132.1)	3 (23.1%)	10 (58.8%)

Table 3 *(cont.)*. Real-life experience on effectiveness and safety of the most frequently prescribed drugs in special situations.

Drug name	Use	Age	ECOG	Treatment duration, days	Effectiveness			Adverse effects					
					Efficacy according to RECIST criteria	PFS	Overall survival	Rate of adverse effects	Toxicity according to CTCAE 5.0	Type of adverse effects	Time to adverse effect, days	Change of treatment due to adverse effects	Successive chemotherapy lines
Off-label use (OLU) drugs													
Pembrolizumab	Cervical cancer (n = 4)	60.5 (SD 14.4)	0: 2 (50.0%) 1: 2 (50.0%)	95.5 (SD 21.9)	CR: 0 PR: 1 (33.3%) SD: 0 PD: 2 (66.7%)	At 12 mo, 50%	P50: 12.8 24 mo: 50%	0	–	–	–	–	0
Irinotecan	SCLC (n = 6)	66.7 (SD 12.1)	0: 1 (25.0%) 1: 3 (75.0%)	96 (SD 62.0)	CR: 0 PR: 0 SD: 0 PD: 6 (100%)	At 12 mo, 0%	P50: 9.5 24 mo: 20.8%	1 (16.7%)	G1: 1 (100%)	Hyponatremia: 1 (100%)	35	0	2 (33.3%)
	Malignant glioma (n = 3)	51 (SD 6.6)	0: 1 (33.3%) 1: 1 (33.3%) 2: 1 (33.3%)	41	CR: 0 PR: 0 SD: 0 PD: 1 (100%)	–	–	1 (33.3%)	G1: 1 (100%)	Diarrhea: 1 (100%)	22	0	0
Compassionate use (CU)													
Durvalumab	NSCLC (n = 18)	68.3 (SD 9.5)	0: 10 (58.8%) 1: 6 (35.3%) 2: 1 (5.9%)	272.5 (SD 144.8)	CR: 3 (20.0%) PR: 3 (20.0%) SD: 3 (20.0%) PD: 6 (40.0%)	At 12 mo, 73.3%	P50: 31.3 24 mo: 76.6%	5 (27.8%)	G1: 3 (60.0%) G2: 2 (40.0%) G3: 0	Immune-mediated hyperthyroidism: 1 (20.0%) Immune-mediated pneumonitis: 1 (20.0%) Immune-mediated nephritis: 1 (20.0%) Diarrhea: 1 (20.0%) Arthralgia: 1 (20.0%)	160.3 (SD 85.9)	2 (40.0%)	1 (6.7%)
nal-IRI	Pancreatic cancer (n = 6)	78.8 (SD 9.8)	0: 6 (100%)	54.8 (SD 48.9)	CR: 0 PR: 0 SD: 0 PD: 3 (100%)	At 6 mo, 0%	P50: 3.4 12 mo: 0%	3 (50.0%)	G1: 1 (33.3%) G2: 2 (66.7%) G3: 0	Loss of appetite: 1 (33.3%) Fatigue: 1 (33.3%) Diarrhea: 1 (33.3%)	83.5 (SD 4.9)	0	1 (16.7%)
Niraparib	Ovarian cancer (n = 6)	67.2 (SD 10.2)	0: 6 (100%)	347.3 (SD 39.5)	CR: 1 (25.0%) PR: 0 SD: 2 (50.0%) PD: 1 (25.0%)	At 12 mo, 80%	P50: – 12 mo: 100%	2 (40.0%)	G1: 1 (50.0%) G2: 0 G3: 1 (50.0%)	Thrombocytopenia: 2 (100%)	35 (SD 5.7)	0	3 (50.0%)

Table 3 *(cont.)*. Real-life experience on effectiveness and safety of the most frequently prescribed drugs in special situations.

Drug name	Use	Age	ECOG	Treatment duration, days	Effectiveness			Adverse effects					
					Efficacy according to RECIST criteria	PFS	Overall survival	Rate of adverse effects	Toxicity according to CTCAE 5.0	Type of adverse effects	Time to adverse effect, days	Change of treatment due to adverse effects	Successive chemotherapy lines
Compassionate use (CU)													
Lorlatinib	NSCLC (n = 5)	53.8 (SD 15.2)	0: 2 (50.0%) 1: 2 (50.0%)	228.3 (SD 186.8)	CR: 0 PR: 1 (20.0%) SD: 1 (20.0%) PD: 3 (60.0%)	At 12 mo, 60%	P50: – 12 mo: 60%	2 (40.0%)	G1: 1 (50.0%) G2: 1 (50.0%) G3: 0	Serum hypoalbuminemia: 1 (50.0%) Depressive symptoms: 1 (50.0%)	331.5 (SD 427.8)	0	3 (60.0%)
Lurbinectedin	SCLC (n = 4)	67.5 (SD 12.0)	0: 2 (50.0%) 1: 2 (50.0%)	72.5 (SD 35.1)	CR: 0 PR: 0 SD: 0 PD: 4 (100%)	At 6 mo, 0%	P50: 7.3 12 mo: 25%	2 (50.0%)	G1: 1 (50.0%) G2: 1 (50.0%) G3: 0	Neutropenia: 1 (50.0%) Pneumonitis: 1 (50.0%)	87 (SD 45.3)	0	1 (25.0%)
Foreign drugs (FD)													
Ethiodol	Hepatocellular carcinoma (n = 58)	69.2 (SD 11.8)	–	–	CR: 12 (60.0%) PR: 0 SD: 5 (25.0%) PD: 3 (15.0%)	At 24 mo, 46.4%	P50: – 12 mo: 95% 24 mo: 77.8%	6 (10.5%)	–	Fever: 2 (33.3%) Pneumothorax: 1 (16.7%) Decompensation with edema/ascites: 2 (33. 3%) Hemoperitoneum: 1 (16.7%)	–	–	–
Lutetium	Neuroendocrine tumour (n = 9)	55.2 (SD 13.4)	0: 4 (44.4%) 1: 5 (55.6%)	195 (SD 84.7)	CR: 0 PR: 2 (28.6%) SD: 4 (57.1%) PD: 1 (14.3%)	At 12 mo, 80%	P50: – 12 mo: 80%	5 (55.6%)	G1: 3 (60.0%) G2: 2 (40.0%) G3: 0	Loss of appetite: 1 (11.1%) Fatigue: 3 (33.3%) Diarrhea: 1 (11.1%)	90 (SD 93.2)	0	1 (11.1%)
Actinomycin D	Rhabdomyosarcoma (n = 2)	22 (SD 4.2)	0: 2 (100%)	42.4 (SD 21.0)	CR: 0 PR: 1 (50%) SD: 0 PD: 1 (50%)	At 12 mo, 50%	P50: 15.1 12 mo: 100%	0	–	–	–	–	2 (100%)

CR: complete response; G1: grade 1; G2: grade 2; G3: grade 3; P50: median OS (overall survival); PD: progressive disease; PR: partial response; SCLC: small cell lung carcinoma; SD: stable disease.

Discussion

Evidence supporting use of drugs in special situations

The level of evidence supporting drugs in special situations is relevant because it is closely related to the expected effectiveness and safety of such treatments. Our study can be used to assess the role of the level of evidence in the decision of application for unathorised drugs for solid tumours.

Despite being considered as an important factor in the use and approval of medicines in exceptional circumstances[10], only a few papers have focused on the evidence that supports the applications of these drugs. Nevertheless, there are several studies analysing the specific drugs approved as "special situation" use. Furthermore, no guidances have been specifically developed to help clinicians assess appropriateness in off-label prescribing. Gazarian *et al.* proposed a classification in order to guarantee the appropriate off-label use: off-label use justified by high-quality evidence, use within the context of a formal research proposal, and exceptional use, justified by individual clinical circumstances[11].

The Spanish Society of Hospital Pharmacy (SEFH) published a survey in 2015 on the use of off-label drugs for Oncohematology patients in Spanish hospitals[10]. The survey showed that the main factor influencing the authorisation-prescription process of these drugs is the available evidence. Nevertheless, a lower level of evidence is usually accepted in cases in which there are no therapeutic alternatives, or in patients with low-prevalence tumours[4]. Also in Spain, Blanco-Reina *et al.* conducted a cross-sectional study in order to determine the level of evidence (according to the criteria by SIGN-NICE) supporting off-label drugs prescriptions in a third-level hospital during 2010. They report 190 applications for off-label prescription and 52.4% were based on some clinical trial, while the rest had a low level of evidence (observational studies and case reports)[12]. In contrast, in our centre 83.1% of drugs in special situations was supported by a RCT. Many reasons could be identified to explain these data. For example, the good level of implementation of drugs in special uses' programs in our context. Furthermore, the existence of unmet therapeutic needs and the rising level of convincing evidence recently, including the growth of adequate and well-controlled trials. Indeed, the proposal and acceptance of applications supported by a high level of evidence could be considered as a sign of proper functioning of these programs.

A study conducted by M.D. Anderson Cancer Centre researchers reported that a third of patients with metastatic breast cancer had received off-label therapy at some point during treatment[13]. Furthermore, an Italian multicenter study revealed that the off-label use in Oncology represented almost 20% of prescriptions, even if most of them were based on scientific evidence of efficacy (one or more RCTs or more phase II trials published in a relevant oncology journal). Addionally, the drugs prescribed were used in a different cancer (46.2%) or for a rare neoplasm (13.6%)[14].

Use of drugs in special situations in cancer patients

Nowadays, 20% of drugs are used off-label, and the percentage is higher in cancer patients. Reasons for the off-label use of drugs in cancer patients include: the wide variety of cancer subtypes, the low prevalence of some tumours, the lack of alternative treatment options, difficulties in enrolling patients in clinical trials, the rapid diffusion of the preliminary results of drug RCTs, and delays in the approval of new drugs by regulatory agencies[4,15].

Only 8% of NCCN guidelines are based on level I evidence. As a result, although lacking strong evidence is usual, oncologists often have to make treatment recommendations[16]. This is particularly important when they make the proposal of an investigational drug use.

Saiyed *et al.* performed a systematic review and noted that among adult patients with cancer, 13%-71% received at least one off-label chemotherapy, mainly because of drug unapproved for specific tumour and modified drug applications. Metastatic cancers and palliative care patients received the most off-label drugs. In addition, the off-label drug use unsupported by standard treatment guidelines was in the range of 7%-31%[17].

Joerger *et al.* performed a study including a total of 985 consecutive patients receiving 1,737 anticancer drug treatments and of them, 32.4% received at least one off-label drug. Major reasons for off-label use were the lack of approval for the specific disease entity (15.7%) and modified application of the anticancer drug (10%)[18]. Conti *et al.* examined the prevalence of off-label anticancer drug use from a population-based cohort database of medical oncologists. In this study, off-label use amounted to 30%. 14% of them were conformed to an NCCN-supported off-label indication. Total national spending on these chemotherapies amounted to $12 billion[19].

According to a prior study conducted in our centre during the period 2005-2008[20], the majority of applications of drugs in exceptional circumstances came from Medical Oncology, Gastroenterology and Rheumatology Department. Montero *et al.* also reported that the majority of drugs in special situations are prescribed by oncologists (approximately 50%)[21].

A study performed in 2002 in France reported that 6.7% of prescriptions presented a drug used in an off-label use. Off-label prescriptions were common in patients with hormone-refractory prostate cancer (57.6%) and in patients with bladder cancer (37.6%). The drugs most frequently used off-label were docetaxel (29%), oxaliplatin (24%), fludarabine (8%) and carboplatin (8%)[22]. In our centre ethiodol (58 applications), used in transcatheter arterial chemoembolization (TACE) for large hepatocellular carcinoma, oxaliplatin alone (21) and durvalumab (20) were the most requested drugs in exceptional circumstances. In addition, in our setting, drugs in exceptional circumstances were most commonly prescribed for hepatocellular carcinoma (13.4%), lung cancer (13.2%) and breast cancer (12%).

The category of some drugs included in this study has changed since the work was done. Some drugs previously considered "special uses" have been approved, reviewed and recategorized over this period, based on the increase of the level of evidence of efficacy, which nowadays is acceptable to support the use of them.

Outcomes in real-life experience

It is important to determine real-world effectiveness and toxicity of these medicines in order to avoid futile treatments in patients with a short life expectancy. Sánchez-Cuervo *et al.* conducted a retrospective observational study to assess the use of chemotherapy over the course of the last 30 days of life. Regarding the patients who initiated a new regimen of chemotherapy during the 30 days before their death, 35.2% of the treatments administered were drugs in special situations[23].

Therefore, we studied real-world evidence about effectiveness and safety of medicines used in special situations. It is crucial to analyse its correlation to the prior available evidence. We discuss effectiveness and safety of the most frequent off-label, compassionate use and foreign drugs below. However, our study has two main limitations: the small sample size of some drugs and the presence of missing values in our data set.

For example, regarding effectiveness and safety of oxaliplatin for advanced gastric cancer, according to our results, mean age of patients was 69.4 (SD 12.3) years and the majority of them (66.7%) had an ECOG PS 1. OS was 10.5 months and 35.7% of patients experienced a disease progression. The most frequently reported adverse event was fatigue (78.5%). These results are consistent with prior studies. Kawada *et al.*[24] reported an OS of 7.1 months (95% CI, 2.3-10.1) and in their study, the most frequently reported grade 3-4 adverse event was fatigue (20%) and hypokalemia (20%).

Palbociclib in combination with endocrine therapy is a valuable emerging option for patients with HR+/HER2– advanced or metastatic breast cancer. In Spain, palbociclib was launched in November 2017, but it was included in an on-going compassionate use programme since 2015. Some real-life studies with palbociclib in advanced breast cancer have been published. Du Rusquec *et al.* informed a SD, PD and PR rates of 45, 28.3, and 26.7%, respectively[25]. The findings of Masuda *et al.* include a 1-year OS and PFS of 92.9 and 75%, respectively[26]. In our study, at 12 months, the PFS rate was 21.2% and the median OS was 17.3 months for patients with very advanced disease, who did not meet label indications for patients with disease progression following hormone therapy. Progression disease rate was higher, 92.3%, in our study, maybe due to the characteristics of patients included (more advanced stage, a higher number of prior chemotherapy lines…), although a limitation of this work is the small sample size (n = 17).

Some studies have addressed the compassionate use of durvalumab in locally advanced and unresectable NSCLC. According to Gil-Sierra *et al.*[27],

the mean PFS was 20.8 (13.6-28.1) months and the mean OS could not be calculated because there were no deaths. They identified 17 adverse events (AEs). The most frequent AEs were: 4 (23.5%) respiratory infections, 3 (17.6%) cough and 2 (11.7%) erythematous lesions. There were 16 (94.1%) AEs grade 1, and 8 treatment interruptions were recorded, without suspensions. In our study, the mean OS was 31.3 months. The rate of grade 1 adverse effects was 60.0%. Durvalumab was discontinued in 2 patients due to adverse effects (40.0%).

Ethiodol is distributed by Guerbet (U.S.) and approved for use in over 47 countries worldwide[28]. A systematic review including 10,108 patients treated with ethiodol TACE have concluded that the response rate was 52.5% (CI 43.6-61.5) and overall survival (OS) was 51.8% at 2 years[29]. Similarly, in our study, response rate was 60%, but OS was higher, 77% at 2 years.

Our findings are consistent with those of Arroyo-Álvarez *et al.*, who analysed the use of off-label oral antineoplastic (ANEO) drugs and oncological outcomes between 2005 and 2015. The median PFS was 5 months (4-21.3), and OS 11 months (9.2-20.6). Moreover, the most frequent reported side effects were asthenia (19%), neutropenia (10.7%), and nausea and vomiting (8.9%)[30]. In the same line, García-Muñoz *et al.* performed a retrospective study of all patients attending the Medical Oncology Department who began treatment with ANEO drugs in 2016. They compare the results obtained with the clinical evidence on which the authorisation was based. They also concluded that the effectiveness of off-label ANEO was similar to the evidence available from RCTs[15]. These data suggest that there are similarities in effectiveness and toxicity profiles in drugs approved for special uses.

In conclusion, a considerable number of drugs in special situations are prescribed to Oncology patients in Spanish hospitals. The majority of applications of drugs in special situations was supported by RCT results. The real-life experience showed an effectiveness and tolerance profile of drugs used in special situations similar to those described in RCTs.

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Conflict of interests

No conflict of interest.

Contribution to the scientific literature

To date, the level of evidence supporting the use of medicines in exceptional circumstances in clinical practice has been scarcely explored in the literature, although it is closely related to the expected effectiveness and safety of such treatments.

This article presents a detailed analysis of applications for drugs in special situations for solid tumours in a representative third-level centre and focuses on evidence supporting these applications, the effectiveness and safety of these drugs.

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