

## Treatment of cancer with oral drugs: a position statement by the Spanish Society of Medical Oncology (SEOM)

### background

Cancer treatment involves the participation of multiple medical specialties and, as our knowledge of the disease increases, this fact becomes even more apparent [1]. The degree of multidisciplinary is determined by several factors, which include the severity and type of disease, the increasing diversity in the available pharmacological and non-pharmacological therapies, and the range of specialists involved in cancer therapy, such as medical oncologists, radiotherapists, gynecologists, gastroenterologists, urologists, surgeons, and pneumologists, among others. Across Europe, the situation of cancer care can be variable due to the diversity of health systems, differences in drug reimbursement, and the degree of establishment of Medical Oncology as a medical specialty in the European Union states [2].

Within this multidisciplinary approach, each of the specialties involved in cancer treatment has a specific role, and according to an international panel of experts, the medical oncologist is the physician who plans global cancer treatment, administers systemic anticancer therapies to the patient, and takes care of the general well-being of the patient [3].

### the use of orally administered anticancer drugs

Oral anticancer drugs have been available since the early days of cancer treatment, although their use had been limited due to, among other reasons, their sometimes unpredictable oral bioavailability, and i.v. agents were preferred. This approach has changed in recent years as a number of cytotoxic drugs such as capecitabine, vinorelbine, or topotecan have become available as oral agents for the treatment of a large variety of tumors like colon, breast, gastric, ovarian, or lung cancer (Table 1). More importantly, the introduction of therapies directed against specific molecular targets has steered the use of oral drugs into the heart of daily oncology practice. Indeed, almost half of the targeted molecules approved for the treatment of cancer in the European Union since the year 2000 are exclusively available as oral formulation (Table 1) [5–8]. Furthermore, the proportion of oral antitumor agents being developed today far exceeds three-quarters of all the cancer therapies that are currently under development [9]. Additionally, some oral anticancer treatments are perceived by most patients as a valuable way to cope with their diseases without many side-effects, visits to the clinic, or

venipunctures [10]. Hence, it is hardly surprising that some cancer patients may prefer the use of oral to i.v. chemotherapy, even at the expense of sacrificing part of the clinical efficacy [11, 12].

### the issue

Along with the growing numbers of oral drugs available for the treatment of cancer, we have observed with great concern that some of these drugs have been moving out of the use by the oncology experts and into that of other physicians that are less familiar with comprehensive cancer treatment. In Spain, we estimate that this practice represents, depending on a particular oral anticancer drug, from ~5% to >20%. This is very likely to eventually pose a risk to cancer patients. The use of oral cancer treatments by physicians unfamiliar with routine oncology practice is worrisome because it compromises the excellence of oncological practice and may result in a deterioration of the medical care received by cancer patients.

Therefore, the Spanish Society of Medical Oncology (SEOM) wishes to state its point of view on this subject to the medical community, with the objective to open a debate, as has been done in the past with other oncology-related subjects as the off-label use of drugs in oncology or the cancer care in the elderly population [13, 14].

### the position statement

The SEOM was founded in 1980, 2 years after the specialty of Medical Oncology was established in Spain [15]. In Spain, the Ministries of Health and Education determine the requirements, the duration, and, above all, the contents of the training programs for each of the medical and surgical specialties, including Medical Oncology [16]. The Spanish training program of Medical Oncology includes all cancer-related issues, namely the molecular biology, epidemiology, diagnostic procedures, the anticancer drugs, and the methodology to be followed in the various types of clinical trials based on the guidelines for Good Clinical Practice. Additionally, Medical Oncology is the only specialty in Spain that covers specifically the pharmacological treatment of cancer using drugs administered i.v., orally, or by any other route. The Spanish Medical Oncology training program has much in common with standards setup jointly by the European Society for Medical Oncology and the American Society of Clinical Oncology [3].

In our opinion, Medical Oncology specialists are presently the best-trained professionals to plan and administer systemic anticancer therapies throughout all European countries in which this medical specialty exists [3]. In addition to Medical

**Table 1.** Oral anticancer drugs approved by EMEA since 2000 [4]

Oral drug	EMEA approval date	Indications
Capecitabine	February 2001	Colorectal cancer, gastric cancer, breast cancer
Dasatinib	November 2006	Chronic myeloid leukemia, acute lymphoblastic leukemia, lymphoid blast chronic myeloid leukemia
Erlotinib	September 2005	Non-small-cell lung cancer, pancreatic cancer
Fludarabine	July 2002	B-cell chronic lymphocytic leukemia
Imatinib	November 2001	Chronic myeloid leukemia, acute lymphoblastic leukemia, chronic eosinophilic leukemia, malignant gastrointestinal stromal tumors, dermatofibrosarcoma protuberans
Lapatinib	June 2008	Breast cancer
Nilotinib	November 2007	Chronic myelogenous leukemia
Sorafenib	July 2006	Hepatocellular carcinoma, renal cell carcinoma
Sunitinib	July 2006	Malignant gastrointestinal stromal tumor, renal cell carcinoma
Thalidomide	April 2008	Multiple myeloma
Vinorelbine	April 2004	Breast cancer, lung cancer
Topotecan	April 2008	Ovarian cancer, lung cancer, cervix cancer

<sup>a</sup>i.v. anticancer drugs approved by the EMEA since 2000: alemtuzumab, bevacizumab, bortezomib, cetuximab, liposomal doxorubicin, liposomal paclitaxel, panitumumab, pemetrexed, temsirolimus, and trastuzumab.

Oncology specialists, there are some physicians in Europe who may be empowered to treat cancer patients. Thus, in some European countries, there are supraspecialists within gynecology, gastroenterology, urology, or pneumology that may have the necessary training to qualify them to treat with drugs certain cancer types, although not all. Also, we must take into account those individual cases of physicians who, although not having formal oncology training, have acquired supervised or unsupervised experience during years of practice.

Why are professionals who are not fully trained or experienced in the pharmacotherapy of cancer prescribing oral antineoplastics? There are several reasons explaining this, among which is the belief that oral anticancer drugs have a lower toxicity, and hence their delivery does not require specific skills or knowledge, or that the administration outside of a day hospital facilitates the outpatient prescription of these agents. Furthermore, the possibility of using novel molecular-targeted drugs may be tempting from a professional point of view because of using ‘modern’ drugs. This is especially true in the field of cancer therapy, which has led the pharmacological molecular revolution that we are witnessing nowadays. In addition, there is a clear marketing pressure applied by

pharmaceutical companies to non-oncology specialists for the use of their latest generation drugs.

Several solid reasons support our warning that the administration of oral anticancer drugs outside the scope of trained oncologists should be considered unsuitable and potentially dangerous.

- It is not true that oral anticancer drugs are less toxic. Although the toxicity profiles of the newer molecularly targeted drugs are less focused on blood cells than those of the traditional chemotherapeutics, they are not, in any sense, insignificant (Table 2). This class of drugs retains the potential for severe and possibly lethal adverse events, whose diagnosis and treatment cannot be properly handled by untrained physicians who do not work in a multidisciplinary environment. Thus, any antitumor therapy, whether administered orally or i.v., whether cytostatic or molecularly targeted, requires safe and careful handling by an experienced specialist and preferably one who has been formally trained in their use.
- The evaluation of the clinical response according to universally accepted criteria is key to anticancer drug administration [17, 18]. Only the training programs in Medical Oncology specifically include this expertise [3, 5]. Furthermore, in some malignancies, such as gastrointestinal stromal tumors, the response criteria used are specifically tailored for a single disease [19]. Physicians, if unfamiliar with the subtleties of oncology practice, may keep administering a drug as long as the patient seems to be tolerating it well, hence confusing ‘clinical appearance’ with ‘clinical response’. In oncology, the term ‘clinical benefit’ means objective response or disease stability in the absence of limiting toxicity [20]. This concept implies carrying out regular and objective evaluations of the tumor’s response to therapy.
- A physician untrained in cancer therapy who decides to prescribe an oral anticancer drug may often administer it as monotherapy because he may feel uncomfortable using the whole range of anticancer agents. Based on wider experience, a medical oncologist will choose the best treatment, either as monotherapy or in combination with other oral or i.v. antitumor drugs, depending on the patient’s situation and the existence of published evidence which supports their use.
- Often, an untrained physician will be familiarized with the use of one oral agent only. For this reason, treatment options offered to a patient may be in these cases just two: either to be treated with that single drug or to be not treated at all. At the heart of a multidisciplinary team that includes a medical oncologist, many treatment options are available. Oral therapy is usually one among several possibilities. The alternatives range from various types of surgeries, radiotherapy, combinations of a variety of chemotherapeutics and biological agents, participation in clinical trials, or referral to an oncology palliative care team. In this era of individualized medicine, cancer treatment in inexperienced hands implies a clear limitation in the chances of tailoring treatments according to the individualized needs of a patient.
- Oncology teams have acquired a particular medical culture founded upon the use of protocols. Not only are anticancer

**Table 2.** Main toxic effects of oral anticancer drugs [4]

Oral drug	Relevant toxic effects
Capecitabine	Diarrhea, vomiting, stomatitis, hand–foot syndrome, pancytopenia, electrolyte disorders, cholestasis
Dasatinib	Pleural effusion, dyspnea, diarrhea, vomiting, skin rash, hemorrhage
Erlotinib	Rash, diarrhea, electrolyte disorders, renal failure
Fludarabine	Pancytopenia, severe infections, vomiting, diarrhea, neuropathy, visual disturbances
Imatinib	Pancytopenia, vomiting, diarrhea, edema, rash, pleural and pericardial effusion
Lapatinib	Diarrhea, vomiting, rash, stomatitis, hand–foot syndrome
Nilotinib	Pancytopenia, diarrhea, rash, pruritus, hyperlipidemia
Sorafenib	Lymphopenia, hypophosphatemia, hemorrhage, hypertension, diarrhea, vomiting, rash, hand–foot syndrome, erythema, pruritus, pancreatitis
Sunitinib	Pancytopenia, hypertension, diarrhea, stomatitis, vomiting, skin and hair discoloration, hand–foot syndrome, rash, epistaxis, glossodynia, decreased ejection fraction, hypothyroidism
Thalidomide	Pancytopenia, peripheral neuropathy, tremor, paresthesia, somnolence, peripheral edema
Vinorelbine	Pancytopenia, neuropathy, vomiting, diarrhea, stomatitis, esophagitis
Topotecan	Pancytopenia, diarrhea, mucositis, vomiting

drugs given according to specific and detailed written protocols but also the administration of complementary therapies, such as antiemetics, bone marrow growth factors, pain management, palliative care, information for the patient and relatives, genetic counseling services, or data inclusion in cooperative databases, is covered by strict procedural guidelines. Outside the area of Medical Oncology, an inexperienced physician often works alone or in small groups, and hence a patient may suffer from inadequate treatment and support.

- We know that anticancer drugs do not benefit all patients in the same way, and many efforts are oriented to the development of biomarkers that make cancer therapy more cost-effective. In a context of finite budgets, it is important that the prescription of these drugs is done by trained specialists that are proficient in treatment selection. Specific policy measures at the European and National levels should conduct strict reimbursement policies that take into account the prescribing physicians' specialty.
- Lastly, in everyday oncology practice, medical therapy and clinical research are so closely linked that it is almost unthinkable to consider them apart. The inclusion of patients in large cooperative clinical trials not only constitutes the best treatment option for many patients but is also a key element in the development of cancer therapy. The sponsors of clinical trials are often either large research cooperative groups or multinational pharmaceutical companies. In these studies, only those professionals who are integrated into solid multidisciplinary teams; who have the infrastructure, the knowledge, the experience, and the motivation necessary to achieve a high recruitment volume; and who demonstrate an

impeccable adherence to the complex research protocols are invited to participate. For patients, being treated outside the oncological expertise may result in missing the opportunity to be included in a clinical trial. For clinical research itself, this may translate into a decrease in the number of patients recruited in clinical trials and in a difficulty in controlling selection bias.

## conclusions

SEOM has observed that untrained physicians outside the Medical Oncology specialty field are prescribing oral anticancer drugs to patients with cancer. This practice is sometimes based on false assumptions about the easiness of administration or the toxic effects profile of the newer oral anticancer drugs. Cancer therapy implies a global responsibility that goes beyond the prescription of a single drug; it is a commitment that encompasses many aspects of the medical care that is offered to a patient and reaches the society as a whole. The responsibility of safe and effective delivery can only be guaranteed within the heart of multidisciplinary teams who have undergone thorough training in all aspects of comprehensive cancer care and who are governed by strict protocols, have wide therapeutic experience, and are either led or coordinated by medical oncologists. We believe that the prescription of anticancer drugs by physicians who are not oncology experts may compromise the current standards of safety and efficacy in the medical care offered to cancer patients and the high quality of cancer research. SEOM wishes to alert our European Medical Oncology colleagues, the European national health care providers, the international oncology community as a whole, and the general public about this situation and to encourage awareness among health care providers. SEOM believes that regulatory measures to deal with this problem should be undertaken both locally and nationally.

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