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The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO)

All drugs need to be given a marketing authorization by a relevant regulatory body in order for patients to receive them [1]. The marketing authorization is granted if the drug is judged to be safe and effective for a given indication following a given administration regimen. This is the drug 'label'. When the drug is used for other indications, it is used 'off label'.

This is different from when a drug is 'unlicensed'. In this case, the drug is not accessible on the market, and, in principle, its use can take place only within clinical studies, or a compassionate/expanded access setting, generally being provided for free by the pharmaceutical company.

The off-label use of drugs in oncology has been estimated to reach 50%, or even more [2–4]. In pediatrics, the off-label issue is particularly widespread, all the more in pediatric oncology [5]. Often, these uses of drugs, although off-label, are fully 'evidence based', and therefore fall within the state of the art. In spite of this, off-label uses of drugs might be viewed as illegal, in a sense. In practice, off-label uses are often 'tolerated' under restrictions, in spite of the size of the phenomenon, especially in some medical areas.

In principle, a drug can be off label under three conditions: (i) because steps to extend the approval have not been made, although evidence of efficacy is available; (ii) because it falls into the so-called 'gray zone' of evidence-based medicine, within which high-level evidence is difficult to reach even for treatments which are likely effective (this may be the case of rare diseases, which do not lend themselves to large clinical studies) and (iii) because the drug is ineffective or at least there is no reason to believe it is effective. Obviously, the off-label issue is of the greatest concern under the first condition, and constitutes a problem under the second, while ineffective treatments simply should not be done.

The off-label issue is more acute in oncology than in other medical areas for some reasons. The main one is the number of cancer types. In fact, each anticancer drug may be useful in several of them. In practice, many widespread anticancer drugs have not got the label for all the indications under which they can be effectively employed. When the drug patent is over, no pharmaceutical company will ever have any interest to pursue any label extension. Rare entities are all the more problematic. With regard to these, benefits are granted to pharmaceutical companies seeking the approval of new drugs for rare diseases, the so-called 'orphan drugs': in essence, economic incentives are guaranteed if the drug is approved [6]. Several anticancer agents are now obtaining the approval as orphan drugs. The mechanism, however, is not a guarantee at all, and in any case applies only to rare diseases. In general, the more specific the label is, the more likely some minor indications may remain uncovered, and this can well occur also if the disease is frequent.

In the end, there is a problem in principle that the approval of a new drug can be sought exclusively by the pharmaceutical company which produces it. If the pharmaceutical company does not have enough interest to pursue the approval on a specific indication, this will be left uncovered, and the use of the drug for such an indication will be off label. The wide diversity of clinical practice adds to this, creating the above-mentioned gray zone of evidence-based medicine [7]. The paradox is that clinical practice guidelines often recommend to use drugs off label, thus outside existing regulatory boundaries, 'against' the law, in a sense. In theory, the reverse should take place: regulatory boundaries should be wider, and clinical practice guidelines should be selective within them.

The off-label issue continuously creates problems to clinical practice, and at intervals may become more acute in one country or another. According to its Bylaws, European Society for Medical Oncology (ESMO) is dedicated 'to promote equal access to optimal cancer care of all cancer patients' [8]. As stated recently by American Society of Clinical Oncology (ASCO) and ESMO, 'health care plans should aspire to meet certain common goals to ensure access to, and the continuity of, quality cancer care' [9]. In regard to the off-label uses of drugs, ESMO believes:

- that the problem of off-label uses of drugs should be urgently addressed and solved positively, when such uses are supported by evidence and amount to standard practice;
- that regulatory bodies should take some responsibility on the off-label issue;
- that, pragmatically, lists of drugs with acceptable indications should be worked out in order to remove them from the off-label area, and in the European Union (EU) this might follow the principle underlying the centralized procedure for approval of new drugs, thus possibly involving the EU regulatory body, the European Medicines Agency (EMEA);
- that, in perspective, new regulatory mechanisms should be searched, by which uses of drugs could be expanded even beyond the initiative of pharmaceutical companies producing them.

The problem needs to be urgently addressed

The persisting need to use drugs off-label constitutes a serious concern. In fact, by prescribing a drug off-label, the physician is asked to take a special responsibility. Formally, he is prescribing something which the regulatory body has not stated is safe and

effective. Therefore, he/she may be called to respond for any problem arising from the use of the drug as if he/she had done something outside the state of the art. Often this is not the case, but the burden of the proof rests on the physician. In any case, the responsibility can be administrative, and third payers may claim that the prescription was not allowed, so that the physician may even be called to reimburse personally or be threatened to do so. Indeed, this may be actually foreseen, although it is often left to the discretion of 'watchdogs' to decide how much to pursue controls. At the very least, physicians may be facing more red tape in order to prescribe off-label drugs. All this can discourage evidence-based prescriptions of off-label drugs. More simply, third payers, whether public (national health systems, and the like) or private, might just refuse to reimburse some off-label drugs, at their discretion. In other words, there is room for improper denials of effective therapies, in an age of mounting health costs constraints. Overall, this might add to existing inequalities in treatment [3, 4, 10].

Regulatory bodies should take responsibility

Regulatory bodies often argue that reimbursing off-label drugs or not is exclusively a matter of third payers. The argument is tenable to some extent, but nonetheless is weak if it implies that regulatory bodies are completely out of the story. The first reason is that, as said above, the implications of the off-label use of drugs are not only financial, but also affect physicians' professional responsibility. Another reason is that third payers, in principle, should 'buy' drugs only from among on-label ones. This is exactly why regulatory bodies do exist: to allow patients and their proxies to find safe and effective drugs on the market. As was said, a 'general off-label use of drugs is the death of the idea of regulation' [11]. Indeed, it is well accepted that regulatory bodies take some responsibility to ensure that effective drugs get to the market even when there are obstacles (thus, for instance, the provisions about orphan drugs). A different argument at the EU level is that these are internal matters of individual states. In the EU, however, anticancer drugs are now subjected to the centralized procedure for marketing authorization of medicinal products, by which the EU regulatory body, EMEA, is responsible for evaluating all the applications, which are centrally made by companies and whose outcomes are relevant for all the EU states [12]. Therefore, the principle of central responsibility for anticancer drugs by the regulatory body, EMEA, is well established in the EU.

Lists of acceptable drugs should be worked out

Pragmatically, tools which make it possible for some patients to receive off-label drugs are in place in some countries, in an effort to overcome a limitation which in the end is only bureaucratic. These tools may well include lists of drugs accepted for selected indications, outside those recognized in the labels, as a very practical way to let patients receive what they need for. In 2006, the ASCO stressed the need to update and fully implement the 'standard medical compendia' used by Medicare in the United States to cover selected, evidence-based, off-label uses of anticancer drugs [2]. As they stated, 'working closely with the cancer community, Congress has fashioned a strong system for identifying medically appropriate cancer therapies, including those that involve off-label uses of United States Food and Drug Administration approved drugs. The system has worked well, as reflected in improvement of cancer morbidity and mortality' [2]. In Europe, states have different policies in regard to the off-label issue, which are often unclear and liable to lead to improper denials. ESMO is carrying out a survey of such policies. There is an obvious need to improve and assimilate them. A powerful solution would be that the EU regulatory body might facilitate the production of compendia of anticancer drugs, enlisting those off-label uses judged to be legitimate.

The initiative of seeking label extensions, or the mechanisms to expand drugs uses, should not depend exclusively on pharmaceutical companies

Medicines for human use are common goods. A high level of social responsibility is implied. A pharmaceutical company may, however, not be willing to pursue label extensions for some of its drugs. Efforts such as those on orphan drugs are to be warmly appreciated, but they may not be enough, since in the end the decision is left to the company, and, furthermore, rare tumors are not the only problem. On the other hand, approving a label extension may not be as demanding as approving a drug for its first indication, first of all in regard to safety. Therefore, while obviously it is only up to the pharmaceutical company to decide whether to bring a new agent onto the market or not, extending an existing label might well follow different rules [11]. Why communities of researchers, the academy, advocacy groups and professional/scientific societies should not have any say in all this in cooperation with the regulatory bodies?

In conclusion, at a time when health expense constraints may easily lead to inequalities in patients' access to available appropriate care, ESMO advocates concrete political steps about the off-label uses of anticancer drugs. Likewise, ESMO wants to support medical oncologists who in this regard find themselves before health administrators or third payers in the need to assert some essential principles of good quality of care.

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