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Actual developments in European regulatory and health technology assessment of new cancer drugs: what does this mean for oncology in Europe?

introduction

The incidence of cancer has been estimated at 11 million cases per year with a global prevalence of 25 million cases, and the World Health Organisation (WHO) has predicted that within the next decade these figures could increase up to 50%, reaching 15 million new cases per year by 2020 [1, 2]. In Europe, there were an estimated 3.2 million new cases of cancer and 1.7 million deaths from cancer in 2008 [2, 3]. As such, there is a current and growing requirement for more emphasis on cancer prevention, research, therapy in general and better targeted anticancer drugs. Rapid licencing and market availability of innovative, more effective oncology drugs are also a necessity.

Inevitably, health care policy makers have to balance between the infinite level of healthcare demands and their finite healthcare resources. This means that oncology drugs have to be assessed not only on their clinical merit, but also on their cost-effectiveness in comparison with currently available alternative therapies. Currently, this system involves input from two different bodies which increases not only the workload associated with drug development, but also the costs. Most EU member states have delegated these so called relative efficacy, relative effectiveness and cost-effectiveness assessments to dedicated health technology assessment (HTA) agencies. Despite commonalities in scope of the assessments conducted by regulatory agencies and HTA bodies, the applied evidentiary and analytical standards, extrapolations from the underlying clinical evidence base as well as scientific value judgements for the same drug differ substantially between the regulatory and HTA agencies [4, 5].

the current system—status and limitations

different assessments by regulators and HTA bodies

Under the current system, new oncology drugs in the EU are assessed under a centralised procedure by the European Medicines Agency (EMA) in the network of over 40 regulatory agencies from all Member States [6]. Based on the opinion of EMA's Committee for Medicinal Products for Human Use, the European Commission decides on granting a European marketing authorisation (European MA), which applies to all EU member states. But, because of the various healthcare systems in the EU member states and the strong subsidiarity principle in the field of health care, each member state negotiates on drug price, reimbursement status and allocated funding independently in light of different healthcare system priorities and affordability. These decisions are made on a national or even regional level and usually are based on a formal assessment of the product by HTA bodies. Examples of HTA bodies are the National Institute for Health and Clinical Excellence in the UK, the Haute Autorité de Santé in France and the Institute for Quality and Efficiency in Health Care in Germany. The principles underlying HTA have been described elsewhere [4, 5, 7].

It is important to note that even if a European MA has been granted, this does not imply that the product will be available to patients everywhere in the EU. If public reimbursement is declined based on the negative result of the assessment by the HTA bodies and corresponding payer decisions, the vast majority of patients will not be able to afford the product.

evidence requirements of regulators

(See supplementary file S1, available at *Annals of Oncology* online.)

use of biomarkers in clinical trials for registration

(See supplementary file S1, available at *Annals of Oncology* online.)

evidence requirements of HTA bodies

(See supplementary file S1, available at *Annals of Oncology* online.)

different approaches across europe

The approaches to HTA vary across different EU countries with regards to evaluative perspective (payer versus societal), the scope of assessments, and more specifically the use of informal or formal cost-effectiveness assessments and methodology as cost per quality of life year gained (QALY) versus other methods, modelling techniques and discounting, and budget impact analysis.

In Germany, for example, drugs are usually available for reimbursed use as soon as European MA is granted. In 2011, the act for restructuring pharmaceutical market statutory health insurance (AMNOG) was introduced in Germany, giving the

licence holder the freedom to set the price of the drug for the first 12 months after launch, only.

(See supplementary file S2, available at *Annals of Oncology* online.)

In most other countries, pricing and reimbursement negotiations precede the broad reimbursed use of drugs which take frequently up to a year or even longer. A major challenge is the interdependence between the prices negotiated in the various countries. As a consequence, prices are much more uniform between member states with different ability to afford innovative cancer care than desirable. As a result of these misaligned HTA, pricing and reimbursement systems, the access to oncology drugs is anything but equal for patients within Europe [http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/cancer-drugs-fund][8, 9].

Adopting different evidentiary and methodological standards may lead to a varying stringency of HTA evaluation. Although direct comparisons between fundamentally different approaches are inherently difficult, general trends can be perceived. On one side, patients in Denmark and Germany appear to have the best patients' access to new drugs due to a more lenient HTA in Denmark and in Germany, the HTA conducted under the remit of AMNOG is not aiming at restricting access beyond the regulatory label but to guide price ('rebate') negotiations. On the other side, the UK is viewed as more stringent but with better cost control [8].

(See supplementary file S2, available at *Annals of Oncology* online.)

Variations in the HTA procedure not only result in divergent prices but also affects the time it takes for new oncology agents to reach the market. Across Europe the average time taken from a drug receiving European MA to market access and thus factual availability for the patients ranges from 0 days as best to more than 450 days in average as worst situation in different European countries [7].

Against this background, formal arrangements between payers and manufacturers with the aim of sharing the financial risk due to uncertainties surrounding the introduction of new medicines have been developed and increasingly utilised for innovative oncology medicines in order to enable earlier access [10–12]. These agreements carry different labels and can take different forms, including price–volume agreements, outcome guarantee, coverage with evidence development and disease management programmes.

Based on the rather mixed experience with risk-share arrangements to date, a multi-stakeholder group facilitated by Tapestry Networks issued a set of recommendations and a framework that supports the constructive engagement of pharmaceutical manufacturers with regulatory and reimbursement decision-makers when addressing remaining uncertainty that can be resolved post-launch http://www.tapestrynetworks.com/initiatives/healthcare/upload/Tapestry_PVA_Working_Group_Recommendations-June13.pdf.

changing the current system

potential improvements

A European HTA procedure should provide a scientifically sound and transparent high quality assessment of a drug's relative clinical efficacy profile. The application for marketing authorisation precedes any HTA assessment. The regulatory assessment by EMA of the benefit–risk is based on the evaluation of the pharmaceutical quality, safety and efficacy and should be a plausible first building block for the subsequent work of HTA bodies. Therefore, at the time of launch, the effectiveness of a drug can only be inferred from efficacy and safety data gathered during drug development which has been the basis of the preceding regulatory approval process. While the comparators used in the HTA may differ between countries and from those that have been used in the pivotal studies and have been considered relevant by regulators, it is more difficult to understand why clinical end points and other clinical trial design elements as well as analytical methods considered valid and reliable by regulators are questioned and sometimes not accepted by HTA agencies and payers. Therefore, a consensual and aligned or at least not contradictory scientific interpretation of the available data by regulators and HTA bodies would be a more consistent basis for local price negotiations and would be an essential ingredient of more consistent patient access to innovative oncology drugs in Europe

EUnetHTA

In 2008, a report by the High-Level Pharmaceutical Forum (HLPF) suggested that the EMA should consider how to further contribute to relative effectiveness assessments of novel drugs. The findings from the HLPF also encouraged the European Commission (DG SANCO) to reconsider its activities and investment into the collaboration of HTA agencies across the EU. Building on the existing elements of EUnetHTA, EC and member states initiated a Joint Action on HTA which among other prioritised subjects was charged with the development of standards in the field of relative (clinical) effectiveness of pharmaceuticals and a related pilot assessment of a drug in 2010. Relative (clinical) effectiveness was considered the most universal HTA domain, hence most eligible for collaborative effort among member state HTA agencies, which explains this particular focus of EUnetHTA [13].

EUnetHTA currently consists of 34 government-appointed organisations from 23 EU member states, Norway and Croatia. An important activity is collaboration with EMA with the objective of identifying opportunities for improving European Public Assessment Reports and making them more useful as a basis for subsequent HTA. Areas of improvement include harmonising structure and the level of details required, the use of standard efficacy tables, data that reflect standard EU treatments, justification regarding the choice of comparator and an explanation of the benefit–risk assessment.

the tapestry network

A second process was initiated in 2010 by Tapestry Networks with the aim of developing and accessing a novel collaborative multi-stakeholder early advice procedure http://www.tapestrynetworks.com/upload/Pilot-report-24-May-2011.pdf []. This initiative was based on the recommendations of disease-specific working groups, convened to develop a shared understanding of value across stakeholders in type 2 diabetes and

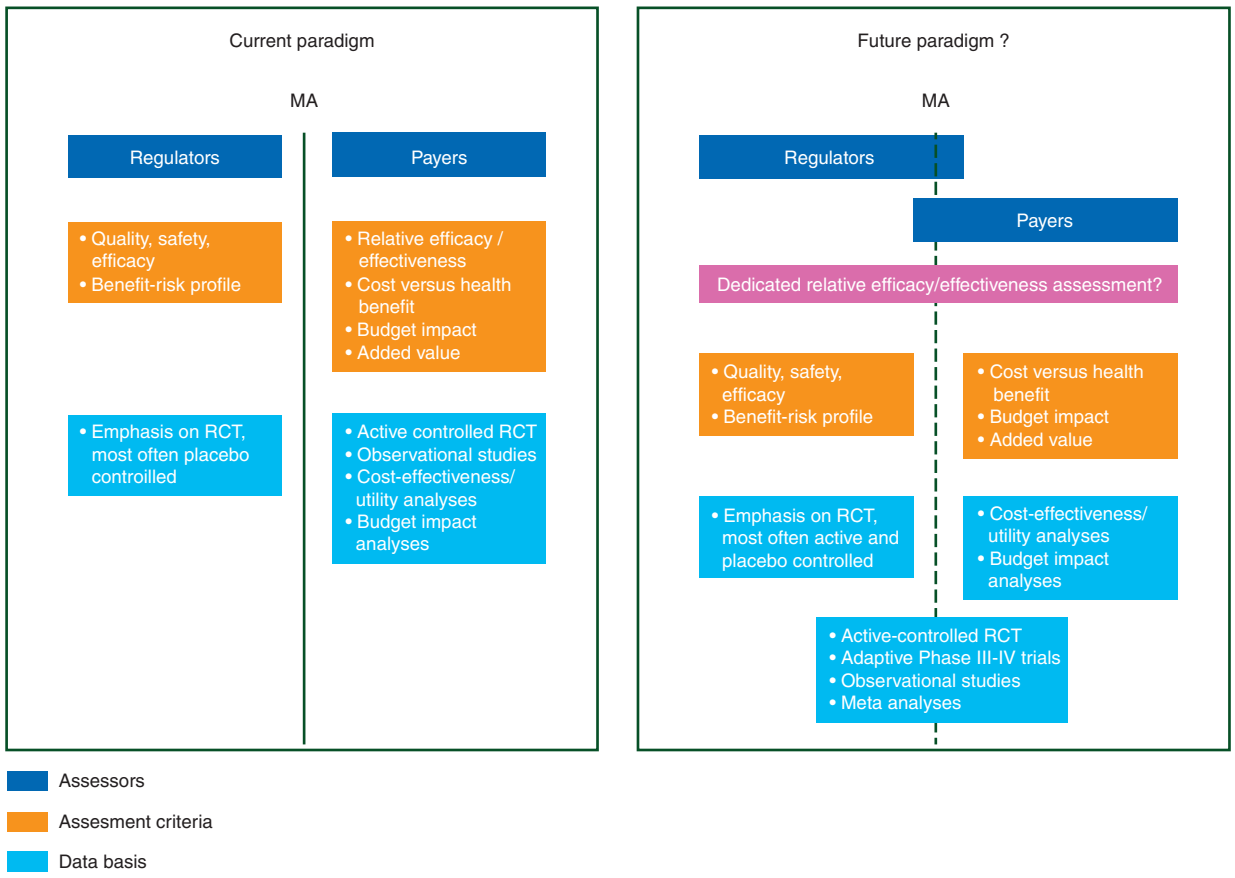

Figure 1. The current (left) and proposed (right) paradigms for the ERB and HTA management of novel oncology drugs. RCT, randomised, controlled studies according to Eichler et al. [14].

breast cancer. The working groups agreed that both public- and private-sector stakeholders in the drug development system lack sufficient information to support and assess the development of innovative medicines that address unmet needs at reasonable cost. They recommended the creation of multi-country, multi-stakeholder consultations as a way to create greater clarity in value assessment to inform development decisions.

European healthcare leaders recently piloted such a multi-country, multi-stakeholder early advice forum, which brought medicine developers together with regulators, HTAs, payers, clinical experts and patient/policy representatives. The advice is used to inform a medicine-specific development plan and inform the best approach to demonstrating a medicine's value (Figure 1, supplementary Figure S1, available at *Annals of Oncology* online). Through six early advice consultations, each involving an innovative medicine in a pharmaceutical company's pipeline, the pilots demonstrated the benefits of early, focused engagement on strategic questions among drug developers and their key European constituencies. After successful pilot projects run by Tapestry, the procedure for parallel scientific advice by EMA and HTA bodies is now available for all applicants and the request need not be made via Tapestry but can be made directly to the EMA and HTA agencies.

conclusions

Based on these approaches, it appears that a system of co-ordination is evolving, in which regulators and HTAs work together using their preferred methodology to assess different aspects of a drug. The continued dialogue and collaboration will help both regulators and HTA bodies to develop scientific positions that may have a different focus without being contradictory or mutually exclusive (Figure 1). These collaborative efforts will also help manufacturers to better anticipate evidentiary expectations and to plan the production of relevant evidence for future oncology drugs at earlier stages in development.

A long-term vision could be a system, in which the EMA and HTA agencies work together to assess the drug based on a pre-agreed effectiveness standard. The EMA should focus on quality, safety, efficacy and risk–benefit; while the HTA agencies/payers focus on the 'value for money' aspect, and the more context-specific HTA domains. Both the groups then come together to discuss relative efficacy and effectiveness based on the data they have obtained [14].

The steps described in this paper to improve the interface between regulators and HTA bodies are promising, but will not be sufficient to overcome heterogeneous HTA assessments between HTA agencies. The current Joint Action on HTA ('EUNetHTA') is an important step towards harmonisation of relative effectiveness assessments and for creating a single

network for improving communication among HTAs and regulators in Europe. Another major issue is—and will remain for the foreseeable future—the heterogeneity of patient access decisions of pharmaceutical payers across Europe which is due to (i) considerably different scientific approaches and methodology to the more or less formal evaluation of cost-effectiveness; (ii) differing health priorities across the countries that reflect historically developed cultural differences and values or different unmet medical needs and (iii) different economic strengths among nations, regions and locales that necessarily drive health care budgetary decisions.

Overall, the first point can be addressed through scientific discussion and exchange to better align drug regulation and reimbursement assessments. The latter two points are even more difficult to overcome and will require fundamental changes in European health care politics. But beyond finding a science-based common position on methodology, greater commitments by politicians and healthcare decision makers will be needed to ensure equal access for patients across the EU to antitumor medicines.

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disclosure

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