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Updating clinical recommendations for breast, colorectal and lung cancer treatments: an opportunity to improve methodology and clinical relevance

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Background: Clinical guidelines can improve quality of care summarising available knowledge and proposing recommendations for health care decisions. Being up to date is one of their quality requisites. Little experience is available on when and how guidelines should be updated. We report on the update process of evidence-based clinical recommendations on anticancer drugs.

Methods: Three multidisciplinary panels, supported by methodology experts, updated the recommendations. The methodologists were in charge of the qualitative and quantitative synthesis of the evidence. The panels were responsible for the final decision about risk/benefit profile of the drugs and strength of the recommendations. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used.

Results: Six recommendations out of 15 were completely updated in 8 months time. In four cases, the strength of the recommendation changed; in two of them, we moved from a weak to a strong positive one. Despite the increased certainty about the positive risk/benefit profile, this was translated in a change in the strength of the recommendation only in one case out of three. Three recommendations were refined making them more clinically specific.

Conclusions: Accumulation of evidence is an opportunity for guideline panels to refine methodological rigour, clinical relevance and to foster consensus on recommendations. This requires time and resource investments.

Key words: anticancer drugs, clinical recommendations, updating process

introduction

Evidence-based practice guidelines (EBPGs) represent a very important tool to improve quality of care as they would stem from a synthesis of available knowledge and contain recommendations that would clearly inform health care decisions. To meet these expectations, EBPGs should be 'valid' and 'up to date'. This means that they have to include all relevant, recent valid evidence and reflect current clinicians' experience as well as patients' value and preferences [1, 2]. Over the last years, a sizeable body of methodological literature on methods of production and implementation of EBPGs has been produced [3–6].

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why it is important to update clinical recommendations

Being up to date is a fundamental quality requisite of EBPGs. Little experience is available to understand how often EBPGs should be updated. In 2001, Shekelle et al. [7] assessed how outdated were 17 guidelines published by the USA Agency for Healthcare Research and Quality: more than three-quarters needed update and the median time to become obsolete was 5.8 years. A similar finding applies also to high-quality systematic reviews (SRs) where the median survival free of signal for update was 5.5 years [8]. These results are not easily generalisable since these samples included both slowly and rapidly evolving fields, which are important factors in determining the stability of evidence. In 2002, Eccles et al. [9] described the process of update guidelines within the North of England Evidence Based Guideline Development Programme concluding that to develop a guideline *de novo* or to update a pre-existing one are similar

considerable tasks. The advantage in efficiency and more manageable volume of evidence of update was set off against the expansion of scope and improvement of methods. The update process did not lead to cost or staff savings.

This paper describes the process and the issues that emerged during the update of the recommendations of the Emilia-Romagna region in the rapidly evolving field of anticancer drugs. We particularly highlight how often the update process led to improving the quality of the recommendations, how it has been obtained and in which aspects the quality remained unchanged or unsatisfactory. The process is described from the perspective of the team in charge of the methodological coordination and the panellists involved, roles and responsibilities, methods and perspective adopted, changes in reporting and synthesis of evidence and in terms of deriving recommendations. The general point of view is that of the Emilia-Romagna Clinical Governance Direction.

methods

In 2005, the Emilia-Romagna Health Care Agency (ERHCA) produced a set of evidence-based recommendations on anticancer drugs identified as around their benefit-risk profile; there was still uncertainty. Specific clinical questions for the treatment of breast, colorectal and lung cancers were developed; a complete description of the process and its implications is described elsewhere [10].

Table 1. Processes and methods

2005—Recommendations' development	2008—Recommendations' update
Development groups	
A 10-person CG—5 members with expertise in oncology and 5 in critical appraisal and narrative synthesis—who oversaw the process. It was responsible for coordinating and chairing panel meetings, undertaking literature search and evidence selection, assessing the quality, preparing the summary of finding tables and drafting the initial version of recommendations.	A 10-person CG who oversaw the process and was responsible for coordinating and chairing panel meetings, undertaking literature search and evidence selection and drafting the initial version of recommendations.
Four multidisciplinary panels, one for each type of cancer and one specific for 'innovative drugs', consisting of 16 medical oncologists and 41 of different medical expertises and patient representatives. They were in charge with the selection of the clinical questions, the evaluation of evidence and the final decision about the risk/benefit profile and the strength of the recommendations.	Three multidisciplinary panels (15% panellists were replaced with alternative ones). They were in charge with the final decision about the risk/benefit profile and the strength of the recommendations. An external MG, skilled in systematic research synthesis and evaluation, was responsible for the retrieving, assessment and synthesis of the evidence. It worked closely with the CG and the three panels through an iterative process, from the refinements of the clinical questions to recommendations' publication.
Type of included evidence	
SRs MAs RCTs	The 2005 inclusion criteria remained unchanged in the update.
Evidence assessment	
Performed by the panellists together with the CG	Performed by the MG
Application of GRADE methodology	Application of GRADE methodology
Summary of the evidence through qualitative tables for each included study	Summary of the evidence at outcome level through structured ToEs using GRADE profiler software[a]
Outcome measures	
A mean number of seven outcomes for each question were selected including efficacy, safety and QoL measures. Nearly all the outcomes were voted has having 'critical importance; except for QoL and few others which received 'moderate importance'[b]	The 2005 outcomes and hierarchy was maintained
Strength of recommendation	
Classified in five levels Strong positive Weak positive Weak negative and Strong negative No recommendation	Classified in four levels: Strong positive Weak positive Weak negative and Strong negative

[a]www.GRADEprofiler.com.

[b]see GRADE criteria for the selection and hierarchy of outcomes [11].

CG, coordinating group; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MAs, meta-analyses; MG, methodological group; QoL, quality of life; RCTs, randomised controlled trials; SR, systematic reviews; ToEs, table of evidence.

In 2007, the ERHCA decided to update the recommendations. The first task was to plan the update strategy taking into account the limits and criticisms identified during the development of the recommendations in 2005. Table 1 summarizes the main features of the process and methods used in the two rounds (2005 and 2008) of recommendations production and update, respectively.

In brief, the main novelties in the update phase were (i) the discharge of the 'innovative drug' panel and the subsequent redistribution of its members into the remaining panels, (ii) the introduction of a methodological group (MG) supporting both the coordinating group (CG) and the panels, (iii) a quantitative syntheses of evidence beside the qualitative presentation of the results of individual studies and (iv) the elimination of the 'no recommendation' option from the categories of the 'strength of recommendations', which forced panellists to take position even in absence of strong evidence. Minor changes were the replacements across all panels of 15% of 'old' panellists who stepped down with 'new' ones.

The GRADE system was used both for the original development and for the update. During the latter, the GRADE profiler (http://ims.cochrane.org/revman/gradepro), a recently released software, drove the assessment and synthesis of evidence in relation to recommendations. This software allows users to develop structured table of evidence (ToEs): every outcome included was quantitatively and qualitatively synthesised following a standardised approach. We never discussed any explicit cost data or cost-efficacy analyses related to assessed interventions.

results

panel process and participation

At the end of 2007, through an email consultations involving all members of the 2005 panels, it was decided that 9 (60%) out of the original 15 clinical questions, involving 10 different drugs, needed updates. Only six got through the complete update process and were released in September 2008. This happened because for two questions (see Box 3), only new unpublished results were found (excluded by our criteria) and for a third one (bevacizumab), it was decided to postpone the publication until the new regulatory indication by European Medicines Agency (EMA) was released.

Overall, each panel had three meetings all-day long. At the first meeting, panellists were informed about the new eligible studies and discussed which studies fully met inclusion criteria and for which outcome the studies provided relevant information. At the second meeting, the CG presented the results of the quality assessment and the quantitative data; their interpretations were also discussed. At the third meeting, panels voted on the recommendations. Meetings were chaired by representatives of the CG. The MG participated in all meetings to solve any doubt or inconsistency about the evidence presented in ToEs.

Tables 2, 3 and 4 illustrate the recommendations in the 2005 and 2008 rounds together with their direction and strength.

Ad hoc search strategies for each clinical question targeted the retrieval of SRs and randomised controlled trials (RCTs). Medline, Embase, CENTRAL and databases for conference proceedings (American Society of Clinical Oncology, San Antonio, ESCO) were investigated. Overall, the total number of records screened was 686; 47 papers were eligible and further evaluated for inclusion (4 SRs and 43 RCTs). In the end, 24 papers (2 SRs and 22 RCTs) were included in the update. This led to the production of 56 ToEs summarising 30 outcomes in total, a median of 5 outcomes for recommendation. Twenty-six ToEs summarised efficacy outcomes and 30 adverse events.

For the majority of questions, results from a single RCT were summarised in the ToEs. Exceptions regarded breast cancer recommendations: (i) taxanes where evidence come from a recently updated Cochrane SRs with meta-analysis (MA) [11]; (ii) trastuzumab where the MG carried out an original MA using the retrieved RCTs and (iii) aromatase inhibitors where the results of an SR with MA [12] and two single RCTs [13, 14] not previously included in that SR were summarised.

Table 2. Clinical questions, benefit/risk profile and strength of recommendations on breast cancer in 2005 and 2008

2005	2008
In women with HR+ breast cancer in postmenopause, are aromatase inhibitors recommended instead of tamoxifen?	
Benefit/risk profile: positive Recommendation: probably use it, weak positive	Letrozolo upfront Benefit/risk profile: uncertain Recommendation: probably use it, weak positive Letrozolo late switch Benefit/risk profile: uncertain Recommendation: probably use it, weak positive Anastrozole upfront Benefit/risk profile: uncertain Recommendation: probably use it, weak positive Anastrozole early switch Benefit/risk profile: uncertain Recommendation: probably use it, weak positive Exemestane early switch Benefit/risk profile: uncertain Recommendation: probably use it, weak positive
In women with positive nodes, should a taxane be used as adjuvant therapy?	
Benefit/risk profile: uncertain Recommendation: probably use it, weak positive	Benefit/risk profile: positive Recommendation: probably use it, weak positive
In women with HER2+ breast cancer (HER2 3+ in immunohystochemistry or FISH test +) without cardiac impairment, is trastuzumab recommended as adjuvant therapy?	
Benefit/risk profile: positive Recommendation: probably use it, weak positive	High risk Benefit/risk profile: positive Recommendation: use it, strong positive Intermediate risk Benefit/risk profile: positive Recommendation: probably use it, weak positive Low risk Benefit/risk profile: uncertain Recommendation: probably use it, weak positive

Table 3. Clinical questions, benefit/risk profile and strength of recommendations on colorectal cancer in 2005 and 2008

2005	2008
In patients with stage II colon cancer, is adjuvant chemotherapy recommended?	
Benefit/risk profile: uncertain	Fluoropirimidine low risk Benefit/risk profile: uncertain Recommendation: probably don't use it, weak negative Fluoropirimidine high risk Benefit/risk profile: uncertain
Recommendation: no recommendation	Recommendation: probably use it, weak positive
In patients with stage III colon cancer, should oxaliplatin be used in association with FU + folinic acid?	
Benefit/risk profile: uncertain	Benefit/risk profile: positive
Recommendation: probably use it, weak positive	Recommendation: use it, strong positive
In patients with metastatic colorectal cancer, should bevacizumab be used in association with FU + folinic acid or irinotecan, FU + folinic acid as first-line treatment?	
Benefit/risk profile: uncertain/positive	Not released[a]
Recommendation: with irinotecan—probably use it, weak positive; without irinotecan—probably don't use it, weak negative	
In EGFR + patients with metastatic colorectal cancer, should cetuximab be used in association with irinotecan after irinotecan therapy failure?	
Benefit/risk profile: uncertain	Benefit/risk profile: uncertain
Recommendation: no recommendation	Recommendation: probably use it, weak positive

[a]The literature search was updated, but the recommendation has been postponed until the new regulatory indication by EMA was released.
EGFR, epidermal-growth-factor receptor; FU, fluorouracil.

Table 4. Clinical questions, benefit/risk profile and strength of recommendations on non-small-cell lung cancer in 2005 and 2008

2005	2008
In patients with stage Ib-II NSCLC, should chemotherapy with cisplatin-containing regimen be recommended instead of nontreatment?	
Benefit/risk profile: positive	Not released[a]
Recommendation: probably use it, weak positive	
In patients with stage IIIa NSCLC, should chemotherapy with cisplatin-containing regimen be recommended instead of nontreatment?	
Benefit/risk profile: uncertain	Not released[a]
Recommendation: no recommendation	

[a]The literature search was updated considering data published in conference proceedings, but the recommendation has been postponed until the studies were fully published in biomedical journals.
NSCLC, non-small-cell lung cancer.

impact of the update on the recommendations

The update process influenced the recommendations in different ways. In two cases, the additional evidence allowed to move the strength of the recommendations from weak to strong positive (i.e. oxaliplatin for stage III colorectal cancer). However, having more information available did not necessarily translate into a change: despite the increased certainty about the positive risk/benefit profile of taxanes for breast cancer from 2005 to 2008 and the overall good 'quality of evidence', the panel confirmed a weak positive recommendation. The decision to rule out the 'no recommendation option' led panellists to agree on a weak positive recommendation in two cases of three (i.e. fluoropirimidine for stage II colorectal cancer in high-risk patients) and led to a weak negative one in only one case (i.e. fluoropirimidine for stage II colorectal cancer in low-risk patients).

In a few cases, the availability of new or additional evidence resulted in an opportunity to refine the original clinical questions allowing for more clinically specific recommendations (directness) [15]. For instance, the question about aromatase inhibitors, originally presented as 'In women with HR+ breast cancer in postmenopause, are aromatase inhibitors recommended instead of tamoxifen?', was transformed into five subquestions according to the type of class agent and administration schedules (letrozole upfront or late switch, anastrozole upfront or early switch and exemestane early switch). Split recommendations referred to more homogeneous trials populations in terms of adopted design and methods and facilitated the grading of the quality of evidence.

In Boxes 1–3, we present in details the cases of three recommendations, one for each type of cancer.

discussion

In 2005, we produced 15 recommendations. In 2008, panellists agreed that nine recommendations required updates and six of them have been subsequently published in 8 months time. Overall, the majority of recommendations that underwent a complete update were somewhat modified (five of six). This was due in part to more information coming from new evidence and in part to the way recommendations were classified (the classification of the strength of recommendations changed from five to four levels, removing the no recommendation option). In particular, three recommendations were refined (trastuzumab, aromatase inhibitors and adjuvant chemotherapy for stage II colorectal cancer) and the questions better specified making them more suitable for application in clinical practice. In two cases (trastuzumab in high-risk population and oxaliplatin for stage III colorectal cancer), the strength of the recommendations was increased, while in other two cases, it remained the same. The main pros and cons of our update experience are shown in Box 4.

During the update phase, a more structured and rigorous process was applied both in terms of the format of the working documents prepared by the MG and in terms of the working procedures and operational definitions. The fact that most

Box 1. Breast cancer: clinical question and recommendation refinements

Trastuzumab is a monoclonal antibody that is used, in association with chemotherapy, for both metastatic and early breast cancer in patients over expressing receptor HER2/neu. The main drawback of this drug could be cardiotoxicity, sometimes severe and persistent even after drug discontinuation. Our recommendation is about its use in early breast cancer. The preliminary results from clinical trials were promising so that in 2005, the panel agreed on a weak positive recommendation (see Table 2). During the update in 2008, more data on the efficacy of trastuzumab were available [16, 17] and the panel decided to refine the original question by splitting it into three prognostic groups—low, intermediate and high risk of recurrence. The recurrence risk was estimated on tumour size and lymph node engagement. This decision was mainly driven by the side-effects caused by the drug. In the end for the high-risk population, the panellists agreed that the risk/benefit balance was highly favourable and issued a strong positive recommendation. In the intermediate group, despite the risk/benefit profile was judge again as favourable, the recommendation turned out to be a weak positive one. In the low-risk group, the majority of panellists expressed uncertainty about the risk/benefit profile because of the few data available for this group and endorsed again a weak positive recommendation.

Box 2. Colorectal cancer: guideline as a starter to launch a new randomised controlled trial (RCT)

In 2004, EMA approved the indication for the use of cetuximab, a chimeric monoclonal antibody against the human—epidermal-growth-factor receptor (EGFR), in combination with irinotecan in the treatment of patients with EGFR expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

In 2005, the panel concluded that 'no recommendation could be drawn' about the use of cetuximab in metastatic colorectal cancer. At that time, the only published study [18] was a phase II study on cetuximab alone versus cetuximab plus irinotecan that showed a statistically significant rate of response (a surrogate outcome) in favour of the combination therapy. Against this paucity of evidence, the panel participated in launching an original phase III trial on cetuximab (FARM6FJJAY), which was funded by the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) in 2006 (www.agenziafarmaco.it). In 2008, waiting for the results of the AIFA RCT, the panel recommended the use of cetuximab on the basis of three trials [18–20]. These evidences were indirect (none of them completely fitted the clinical question) and flawed. Nevertheless, following the majority rule, the recommendation turned out as a weak positive one.

Box 3. Non-small-cell lung cancer (NSCLC): possible use of unpublished literature to make recommendation

Until recently, the benefit of adjuvant chemotherapy in stage I-IIIA NSCLC patients was uncertain. Our recommendations were about the use of adjuvant cisplatin-containing regimen in NSCLC in stage Ib-II and IIIa. In 2005, they turned out as a 'weak positive' and a 'no recommendation', respectively. These judgments were made by the panel according to the benefit and risk profile derived by four 4 meta-analyses and 14 single trials (http://asr.regione.emilia-romagna.it/wcm/asr/ric_inn/prier/gr_v/pr_oncologia/stpr_farmaci_onco/raccomandazioni.htm). During the update, two original large-scale systematic reviews (SRs) were identified on conference proceedings [21, 22] and were only available in abstract form. These SRs presented more robust evidence. As a general rule, before starting issuing the recommendations, the panels decided that only published results would have been used for the recommendations [23]. Nevertheless, it was decided that access to preliminary data or ongoing publication would have represented a benefit. The coordinating group, connected with many research international groups, contacted the SRs' authors having then access to the ongoing publications. The methodological group prepared the table of evidence using the unpublished data so that the panel could access to the preliminary results. Finally, the panel decided to postpone the release of recommendations until full publication of SRs. This case represents how panellists may feel the conflicting tension between the usage of novel data and the responsibility to give to these results a pioneer value for clinical practice.

Box 4. Our update experience

Pros

- Better adherence and relevance of the recommendations to the everyday clinical practice
- Improvement in the methodology adopted and in the structure of the final documents;
- Positive collaboration between clinicians and methodologists, which allowed a mutual sharing of knowledge and experience.

Cons

- Increasing in the number of people involved in the process;
- No relevant time savings.

panellists (85%) served both in the 2005 and in the 2008 round allowed the update process to take advantage of a group with a better understanding of its task and of the methods used as they already were familiar with all phases of the activities. As shown in other experiences [24], the input coming from the panels not only allowed to develop recommendation consistent with the evidence but also oriented to the ordinary practicing of the oncologists. Moreover, the fact that the panels' members are all coming from the oncological community of the Emilia-Romagna region could help in the final adoption of the recommendations [24].

The update, however, was neither time nor resources saving. As in Eccles et al. [9] study, it seems that the improvement in methodology (i.e. development of original MAs) and tools (i.e. ToEs developed using GRADE profiler) led to an increase in people involved and in time needed to complete a rigorous process.

The use of the GRADE system for the update followed the encouraging experience of 2005 [10]. Main insights proposed by GRADE are (i) a clear demarcation between the concepts of quality of evidence and strength of recommendations, (ii) the introduction of new dimensions as indicators of quality of evidence (i.e. consistency, directness) and (iii) the outcome level as opposed to study-specific assessment[15]. All in all, this is intended to bring greater transparency to the whole process going from SRs to formulation of recommendations by expert panels. These achievements are so promising that different international organizations (i.e. World Health Organization)

have started to use GRADE to produce their guidelines and the Cochrane Collaboration is implementing the GRADE's Summary of Findings format to improve and standardise the outputs of its SRs [25, 26]. However, the application of this method is challenging and needs optimal skills and experience in clinical epidemiology and research methodology. In 2005, the criteria adopted by panellists to judge the quality of evidence, the net benefit of drugs and the strength of the recommendations were extremely variables [10]. Guideline panels critically appraised the quality of the RCTs in a free format discussion and such process was obviously vulnerable to different types of bias. Therefore, a more systematic and explicit approach was deemed necessary to reduce variability among panellists, value minority opinions and foster communication of this information. The support of the MG in the retrieval and assessment of the evidence allowed systematisation and reproducibility to the update process, but this cause an increase in terms of people and expertises involved.

Moreover, in 2008, the GRADE Working Group released the GRADE profiler software: this led to a considerable amount of additional work because the studies already included in the 2005 recommendations had to be standardised according to the new format too. The ToEs alone were initially supposed to be self-explanatory for the synthesis of studies, but at first sight, they were perceived as rather unfriendly by panellists. It was therefore decided to provide panels with descriptive tables for each included study and main results were always presented by clinical epidemiologists during face-to-face meetings to facilitate discussion and deeper understanding.

Ideally, the update process should take advantage of the availability of more evidence matured after the first edition. Unfortunately, in the rapidly evolving field of anticancer drugs, new drugs are often registered and introduced in the market with limited evidence of effectiveness and safety (i.e. only one or two RCTs), SRs are rarely available or up to date requiring that *ad hoc* SRs are carried out or at least updated. The update process indeed may help to overcome criticisms emerged during the initial development when evidence was still largely immature, but it does not always solve the uncertainty. For example, during the production of the recommendation on cetuximab, the CG and the panellists had different views that remained the same also after long discussion (Box 3). This particular case highlights the differences in intellectual paradigms and decision rules between different partners (methodologists, frontline clinicians, licensing authorities and policy makers) [27]. In our update, the final decision about the strength of the recommendations was always the result of a split vote that could be solved using a rigid majority rule; the CG and the MG never voted.

conclusions

New anticancer drugs represent a difficult topic for guidelines because of the rapid evolution of knowledge in this field and because new drugs are often approved and registered with limited evidence available [28–31]. Besides allowing the incorporation of new evidence if available, the update process allowed us to refine the methodology of critical appraisal, the quantitative synthesis of the studies and the directness of the recommendations, but the time and resources needed to complete the exercise were not lees as it could be expected.

Few empirical data, about the rate at which clinical practice guidelines become outdated is available and there is a lack of practical methods for assessing guidelines for current validity [6].

Given the different speed of evolution of the evidence in different medical fields, research on the methodology of guideline update should focus particularly on the survival time of research products.

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disclosure

None of the authors declare conflicts of interest.

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