French Health Technology Assessment of antineoplastic drugs indicated in the treatment of solid tumours: perspectives for future trends

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BACKGROUND
- In the past, oncology area enjoyed from a relatively lenient price and reimbursement environment compared to other therapeutic areas, while cancer was perceived as a lethal disease with limited treatment options.
- Today, patients are surviving much longer with new treatment alternatives and more personalised approaches.
- In the context of economic crisis, French Health Authorities, as other European countries, implemented various measures to keep pharmaceutical expenditure under control and highly scrutinise the market access of innovative medicines such as antineoplastic drugs [1-4].

OBJECTIVES
- To conduct a review of the Transparency Committee (CT) (French Health Technology Assessment (HTA) Body) opinions on antineoplastic drugs indicated for the treatment of solid tumours to foresee future HTA requirements in France, and more specifically:
  1. To assess current trends in French health technology assessment (HTA).
  2. To confront experts with outcomes of this review.

METHODS
- We performed a review of the CT opinions issued for all antineoplastic drugs indicated in the treatment of solid tumours and approved over the last 6 years (2009-2014):
  - Identification of medicines having a centralised marketing authorisation between 2009 and 2014.
  - Identification of all drugs for the treatment of solid tumours and extraction of CT opinions.
  - Based on the extraction, descriptive statistics and qualitative analysis were performed. Products that were scored ASMR* 1, II, III (improvement in actual benefit) were considered as presenting on additional benefit acknowledged by the CT.
- The secondary research was complemented by an expert board consultation with five experts with significant experience in French HTA decision making in oncology to capture the critical issues on the future of antineoplastic drugs HTA.

RESULTS
- Thirty-one drugs indicated for the treatment of solid tumours were identified. Targeted therapies represented 77% of all drugs. The main characteristics of the selected drugs are presented in Figure 1.

Review of CT opinions
- Initial CT assessments were available for 26 drugs:
  - For initial CT assessments, 4 drugs had insufficient actual benefit (SMR*) not recommended for reimbursement.
  - Drugs with insufficient SMR, improvement in actual benefit (ASMR**) ratings granted were respectively of V, IV, III and II for 8 (30%), 10 (37%), 5 (18%), and one drug (4%) (Figure 2).
  - Early access scheme for innovative medicines did not predict ASMR score (Figure 2).
- Efficacy/safety ratio predicted SMR, but not ASMR ratings (Figure 3).

Figure 1. Drugs characteristics: Tumour type (A), Number of indication (B), Administration mode (C), Pharmacologic class (D)

Note: Data reported for 31 drugs indicated in solid tumour having centralised EU marketing authorisation, 2009-2014
* 1 drug targeting 2 types of cancer and 1 drug targeting 2 types of cancer

Figure 2. ATU status, ASMR and SMR ratings
A. Drugs with ATU per ASMR decision
B. Drugs per ASMR ratings
C. Drugs per SMR ratings

Four key items in CT assessment were identified:
1. Clinical trial methodology
   - Preferred design: Double-blind clinical trial versus active comparator, when possible.
   - Post-hoc analyses usually rejected.
   - Even for orphan drugs, study methodology is highly scrutinised.
2. Acceptance of progression-free survival (PFS) as a valuable endpoint while overall survival (OS) remains a key endpoint
   - Improvement in OS by 3 months or more versus comparator may lead to a substantial SMR and high ASMR (e.g. ASMR II for trastuzumab emanisine in breast cancer; 65-8 months).
   - However, ASMR III might be granted even if not significant results were found for OS.
3. Transferability of clinical outcomes in clinical practice
   - The transferability of study results can be questioned if the study patient characteristics and standard of care do not reflect current clinical practice.
   - Limited duration of the study and uncertainty on the drug safety can also negatively impact CT decision.
4. Unpredictability of CT decisions
   - The CT may provide unpredictable opinions, taking into account a vast array of contextual elements (e.g. reimbursement granted with studies versus placebo while pertinent comparators exist; ASMR granted on overall study population despite the comparator is not licensed for one of the subgroups and that study results differed between subgroups; reimbursement granted even if doubts remain on non-inferiority versus the comparator and available treatment alternatives).

Critical clinical trial and methodological considerations
1. Increased survival in oncology
   - Importance to robustly validate PFS as a predictor of OS.
   - Quality of life on top of life extension becoming a critical factor.
2. Increasing use of cross-over designs
   - Requiring to adopt statistical models for adjustments: Level of payer adoption?
3. Fast development of available therapeutic alternatives
   - Increasing importance of indirect comparisons.

Health economic will continue to develop in France with methodological requirements expected to increase

CONCLUSIONS
- French system remains committed to its values and philosophy (access of all innovations for everybody) which are threatened by the increasing launch of innovative therapies and budget constraint.
- French HTA analysis decision model will have to evolve to cope with new challenges raised by oncology drugs.
- More coordination is expected between the European regulators, payers and pharmaceutical companies for evidence generation.

References