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Journal of Liver Research, Disorders & Therapy

Opinion

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Options for end-stage liver cancer: A fresh approach

Keywords: hepatocellular carcinoma, sorafenib, chemotherapy, liver surgery, interventional oncology

Abbreviations: HCC, hepatocellular carcinoma; TARE, trans-arterial radio embolization; SIRT, selective internal radio embolization; EMA, european medicines agency; HTA, health technology assessment; CERGAS, centre for research on health and social care management; ICIR, italian college of interventional radiology

Volume 3 Issue 7 - 2017

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Received: November 22, 2017 | **Published:** December 08, 2017

Opinion

Sorafenib is still the only approved first-line therapy for advanced stage hepatocellular carcinoma (HCC). It was introduced several years ago.[1] But has limited activity (mainly disease stabilization) and a modest impact on progression-free and overall survival. It also has considerable toxicities, leading to dose reduction or treatment discontinuation.[2]

Neither reduction of the starting dose nor the introduction on the market of regorafenib in second line has added much in terms of efficacy or tolerability.[3,4]

Minimally invasive loco-regional procedures, in which local efficacy is maximised, and in the same time systemic toxicity is minimised, are often used in the curative or palliative treatment of HCC; different types of approaches are indicated for the different stages of the disease, and most are included in the current guidelines (EORTC Clinical Practice Guidelines, American Association for the Study of Liver Diseases, European Society for Medical Oncology, Barcelona Clinic for Liver Cancer) for early or intermediate stage disease.

TARE (trans-arterial radio embolisation), also known as SIRT (selective internal radio embolisation), is an Interventional Oncology procedure in which the necrotising agent (beta emission from Y90) is delivered to the tumour intra-arterially through selective catheterisation; it is currently used in clinical practice in many countries in advanced-stage HCC. In spite of over 10years of clinical experience, TARE is still not explicitly recommended in the clinical guidelines, and currently considered experimental. Because of this, it is still offered only to a minority of patients, even if it associated with good patient acceptance, good Quality of Life, and efficacy comparable to that of sorafenib in many clinical circumstances.

The absence of TARE from accepted guidelines, and the consequent limited number of referrals from medical oncologists, is mainly due to the relative lack of solidity of clinical evidence. This is true, possibly, for two reasons:

i. The challenges in applying to IO clinical trials the standards established by clinical trials of chemotherapy.

ii. The regulatory framework for medical devices, often not conducive to the setup of adequate clinical trials.

The latter issue is currently being addressed by legislative changes, which will hopefully render the approval of sophisticated medical devices (such as those used in Interventional Oncology treatments) more dependent on adequate level of clinical evidence. The former issue is currently being addressed by a group of physicians involved in different capacities in Interventional Oncology, together with the Oncology Department of the European Medicines Agency (EMA). The work of this group is still in progress, however preliminary consensus statements (the "Canary Wharf statements") include among the significant Endpoints in Interventional Oncology studies also Quality of Life, Activities of Daily Living and other Patient-reported Outcomes, and Health Economics assessments.

Health Economic assessments are too often confined to the final stage of market access; this is unfortunate, because, especially in the case of complex comparison between different entities (in our case, sorafenib and TARE), an early Health Technology Assessment (HTA) would lead to extremely interesting results, and, perhaps, to substantial changes in clinical practice.

A common definition of HTA is "a multidisciplinary approach that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner".

This is based on clinical data, on Quality of Life data, and on an economic evaluation. Economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences". The evaluation is ideally built around two elements:

a. A cost-effectiveness analysis.

b. A budget impact analysis.

For all these reasons, the recent collaboration between two prestigious Italian groups, the Department of Surgery, Liver Surgery, Transplantation and Gastroenterology of the Istituto Nazionale Tumori (National Cancer Institute) and the Centre for Research on Health and Social Care Management (CERGAS) of the Bocconi University, both in Milan, Italy, is an extremely welcome event.

In 2014 the two groups set up to assess the evidence for TARE in advanced HCC, with the collaboration of a number of other clinical centres in Italy performing the procedure; and then proceeded to perform a Cost-Effectiveness analysis and a Budget Impact Analysis of the two approaches.[5–7]

Additionally, Prof Tarricone of the Centre for Research on Health and Social Care Management (CERGAS) and the Department of Policy Analysis and Public Management, both of the Bocconi

University, presented preliminary results at the ICIR (Italian College of Interventional Radiology) Congress in Milan in October 2015, and Dr Bhoori of the Department of Surgery, Liver Surgery, Transplantation and Gastroenterology of the Istituto Nazionale Tumori (National Cancer Institute), Milan, presented the results at the ECIO (European Conference on Interventional Oncology) conference in Bilbao in April 2017. In both cases the presentations were welcomed – by a purely clinical audience- with extreme interest.

The results, in terms of Cost-Effectiveness, can be thus summarised: for intermediate-stage patients, "the model estimated for TARE versus sorafenib an incremental cost-utility ratio of €3,302/QALY (incremental cost-effectiveness ratio of €1,865 per life year gained), whereas for patients in advanced stage TARE dominated (lower costs and greater health improvement)". In terms of Budget Impact, the group hypothised "different scenarios, at 1, 3 and 5years, with reasonable increased use of TARE (30%, 40% and 50%), revealing a potential decrease in the healthcare budget after the diffusion of the new medical device based therapy, thus supporting the economic sustainability of radio embolisation in comparison to sorafenib in the relevant population".

Whilst there are many precedents of Health Economic Evaluations in this field (just worth mentioning Gramenzi A et al.[8] from the Bologna group, and Salem R, Lewandowski R of the Chicago group), a structured collaboration of this scope between a reputable centre for Liver Surgery and a reputable centre for Health Economics seems unprecedented.[8] It is also worth remembering that, whilst this research was conducted in a specific geographic and health-economic environment (Northern Italy in the years 2014-2016), and on a limited number of patients (308 propensity-scored matched patients), the results are, mutatis mutandis, often generalisable to a global scale.

This kind of collaboration sets a precedent of momentous importance: the addition of the key economic factor to the clinical package, as part of a revised prioritisation of key endpoints in the generation of clinical evidence, can modify substantially the future generation of guidelines, and therefore clinical practice. More importantly, the highest benefit will be for HCC patients, who will be able to benefit from the best treatments, as assessed in a more open and rational way.

Disclosures

Consultancy fees from Astellas, Biocompatibles, Biopheresis, Brovedani, BTG, Clasado Biosciences, Second Sight, Terumo.

Board memberships

Seventeen, BetaGlue Technologies.

Acknowledgements

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

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