Opinion

Interstitial beta-ablation: in search of the Holy Grail

Volume 4 Issue 2 - 2018

Lucio Fumi,[1] Massimo Castellani[2]
[1]Wyfold Medical Consultancy, UK
[2]Ospedale Maggiore Policlinico, Italy

Correspondence: Lucio Fumi, Wyfold Medical Consultancy, 2 Wyfold Cottages, Wyfold, Reading, RG4 9HX, UK, Email Lfumi@aol.com

Received: April 09, 2018 | **Published:** April 17, 2018

Introduction

In recent years, the clinical success of both Percutaneous Ablation (PA), whether through Ethanol Injection, Cryo-Ablation, Radio-Frequency or Micro-Wave techniques; and Selective Internal Radio Therapy (SIRT) has lead a number of researchers in Interventional Oncology around the world to try to combine the two procedures.

The aim is to provide a treatment of neoplastic lesions by combining the practicality and immediacy of a percutaneous approach with the clinical efficacy of Internal Radiation. The added value of this potential therapeutic approach is that these combined techniques could reduce the incidence of reoccurrence of cancer, not uncommon with the traditional ablation procedures, and therefore increase Organ-Specific Progression-Free Survival, and in selected cases also Progression Free Survival and Overall Survival.

As the necrotising effect is achieved with beta-emission from a number of different radio-active isotopes delivered directly into the tumoral lesion, rather than through the traditional intra-arterial route, this treatment is often called "Interstitial Beta-Ablation". The definition "interstitial" is not totally correct, however: a needle large enough to deliver the radio-active isotopes and their vehicle will inevitably cause cellular damage, both in the tumoral lesion and in the healthy parenchyma it has to cross to reach the lesion; in other words, it is not just the interstitial space that is the target of the injection. Alternative definitions have been used, such as "parenchymal" and "intratumoral", even if this latter definition is often used also for intra-arterial approaches. Organs other than the liver can be targeted: pancreas, kidney, lung and breast have been considered. The percutaneous route, furthermore, is not the only one used: intra-operatory and peri-endoscopic routes are being investigated, depending on the target organ.

If the concept seems straightforward, the reality is however much more difficult. The search for the right technique and procedure, carried out by numerous groups around the world in the last 20 years (as shown by the number of patents filed and granted), can perhaps be compared to the search for the Holy Grail carried on by the Arthurian Knights in the Middle Ages.

Indeed, a more effective form of Percutaneous Ablation (with potential elimination of all the micro-satellite metastases, and therefore the incidence of re-occurrence of the neoplasia in the short or medium term) can be alluring. But the technicalities involved are complex, and, so far, no researcher seems to have had the success they were hoping for; even if publicly available information (such as that contained in websites) shows that some might be close to market.

There are a number of technical, clinical, and legal issues in this field of research. They can be summarized as follows:

a. Radio-active isotope chosen.
b. Its chemical form (free salt or bound to the surface of microspheres).
c. Beta-emitter or beta & gamma-emitter.
d. Vehicle: glue, diluent, volumes injected.
e. Physical consistency of the neoplastic mass
f. Chemical and physical stability of the isotope in the vehicle.
g. Delivery device: pressure of injection, routes of injection, volumes of injection.
h. Regulatory status.
i. Intellectual property.

a. Radio-active isotope

Given the experience from intra-arterial procedures in SIRT, the most common radio-active isotopes chosen so far have been Yttrium 90, Holmium 166, Phosphorus 32, and Rhenium 188. They are all beta-emitter (some also gamma-emitter, see below) and the main parameters to be considered are energy of emission, depth of penetration, lethal radius, half-life. Different choices can be made, depending on the target organ, the histology and the biology of the target lesion.

b. Chemical form

Most of the isotopes described above have been studied for intra-arterial injection, and therefore bound to the surface of plastic, resin, silicon, poly-lactic acid, etc microspheres, or included in the matrix of glass microspheres. The available microspheres, with an average diameter of 30 microns, are specifically designed for intra-arterial use, where they wedge into the arteriolae of and around the tumoral lesion. They are, however, very large for a proper interstitial injections, and this must be taken into account.

Isotopes can also be delivered in saline form, dissolved in a diluent or matrix; this choice allows for much smaller particles (diameter much smaller than 1 micron, and therefore permitting a real "interstitial" delivery). The issue is both technical and of regulatory nature: whilst the microspheres are classified as medical devices, the isotopes salts are classified as drugs, unless the diluent or matrix has appropriate characteristics that prevent the leakage of isotopes outside and beyond the tumoral lesion.

c. Gamma emission

Some of the isotopes listed above are pure beta-emitters (Yttrium 90, Phosphorus 32), other (Holmium 166, Rhenium 188) have also a low-energy level of gamma emission. This can be extremely useful for

diagnostic purposes (the anatomical site of delivery can be detected with accuracy, and in real time, with standard imaging techniques), but poses logistical and regulatory issues – post-intervention patient isolation, for example – that must be taken into account.

d. Vehicle

Radio-isotopes delivered through microspheres are normally suspended in water for injection. This must be taken into account as it increases the volume of the injected material. In the specific case of interstitial injections, moreover, a matrix must be used that keeps the injected microspheres in place, avoiding spillage and leakage outside the tumoral lesion. A matrix is necessary, of course, also in case of isotopes delivered as salts. Whether this matrix is surgical glue, a diluent, or a different vehicle, a number of parameters must be kept in mind: its capacity for retention, its potential chemical interaction with the isotopes, and the total volume of the injection. The latter has a particular importance in case of injection into compact and hard tumoral lesions, with very limited tissue compliance.

e. Consistency of the neoplastic mass

The histology and the physical consistency of the neoplastic mass can vary considerably. In the liver, HCC lesions tend to be soft and often surrounded by a pseudo-capsule; secondary lesions from colorectal cancer, for example, tend instead to be harder and have no capsule. Neuro-endocrine tumours tend to be soft; pancreatic cancers tend to be hard. As mentioned above, this aspect has a considerable impact on the decisions made in the development of intra-tumoral necrotising injections. Soft lesions will be more compliant, and accept larger volumes; harder lesions will require instead much smaller volumes.

f. Stability of the isotope in the vehicle

Both in case of isotopes injected as salts, and of isotopes bound to the surface of microspheres, any type of chemical or physical interaction between the isotopes and the vehicle must be taken into account, as it can have an impact on the leakage outside the anatomical space of the lesion, or it can modify the properties of the vehicle, of the isotope, or both.

g. Delivery device

Delivery devices are of course different depending on the route of intra-tumoral injection, whether percutaneous, intra-operatory or peri-endoscopic. In all cases, though, the lumen of the needle must be small enough to be able to cross the healthy parenchyma causing as little disruption as possible, and in the same time to penetrate into the lesion as desired. It must be, on the other hand, large enough to allow the passage of the microspheres (if this is the form chosen) and the vehicle. For the latter, its volume, density, and viscosity must all be considered.

h. Regulatory status

As mentioned above (point 2), whilst the microspheres are classified, in all regulatory geographies, as medical devices, the isotopes salts are classified as drugs. This is justified by the fact that they are normally administered systemically. If, however, the vehicle, diluent or matrix has appropriate characteristics that create a confined physical environment around the isotopes, by solidifying instantly when in contact with the interstitial fluid, this can prevent the leakage of isotopes beyond the tumoral lesion, and might allow the classification of the system as a medical device.

i. Intellectual property

A large number of patents, of different levels of quality, have been granted worldwide in this field of research. Some of them contain overlapping, unreasonably comprehensive, unsubstantiated or contradictory claims; which can perhaps question the reliability of Patent Agencies, or even the concept of patent itself, as some thinkers maintain. It must also be recognized, though, that the relevance of patents is mostly limited to the inventor, and to the Venture Capital firms that back the development of the invention. What probably matters to the clinician, to the manufacturer, and – most importantly – to the patient, is that the right, safe and effective product is placed on the marked and made available to Interventional Oncologists in a timely manner, and is backed by a solid package of clinical evidence.

The Holy Grail might indeed exist, but we have not found it yet.

Acknowledgements

None.

Conflict of interest

There is no conflict of interest.