Another modality to treat esophageal cancer?

Minimally invasive endoscopic therapy has come of age in the last decade. We now treat dysplastic Barrett's esophagus very effectively with endoscopic resection and radiofrequency ablation. Endoscopic submucosal dissection is increasingly used for early squamous cancers and also for spreading dysplasia within the esophagus. For locally advanced disease in both squamous and adenocarcinomas, chemoradiotherapy followed by surgery has, in the last few years, become a standard therapy [1]. But how do we help people who do not fit the criteria for surgery or who develop recurrent disease, for whom very few treatment options remain? In this edition of GIE, Yano *et al* continue their work in this area. They report here on their experience of photodynamic therapy (PDT) as a salvage therapy for patients who have previously undergone chemoradiotherapy for squamous cell cancer of the esophagus (REF GIE 2016).

PDT involves the administration of a photosensitizing agent, usually by intravenous injection. The agent is then activated by light applied to the selected area. A low-power laser is used to avoid heating the tissue. The agent absorbs the energy from the light, and this results in the formation of highly active singlet oxygen. This interacts with tissue leading to apoptosis and necrosis through a photochemical effect. This approach leads to a highly targeted therapy which can be delivered as day case treatment and offers the possibility of repeat treatments. There are, however, significant limitations. Firstly, the drugs produce skin photosensitivity which, for older drugs, like the porfimer sodium used in this study, can last for months. Tumor selectivity is achieved by shining the light in the correct place, but where normal tissue is illuminated, non-specific destruction occurs, and although it is claimed that there is no scarring, the reality is that it often does occur. The promise of a gentle, repeatable therapy has not been borne out so far in practice due to the complex parameters that need to be optimized. Laboratory research continues to develop in both scope and extent, but very few clinical trials have yet been undertaken successfully.

There are no randomized controlled trials (RCTs) of PDT for esophageal cancer and very few in any other cancer type. In fact, the most important RCT was the one which showed the value of PDT using the first generation drug, porfimer sodium (Photofrin), to eradicate high grade dysplasia in Barrett's esophagus (BE), which was published in GIE [2]. Our group later compared porfimer sodium with the shorter acting 5-aminolevulinic acid (ALA) and although neither drug was particularly successful in our study, ALA did have fewer side effects [3]. PDT is no longer used but this work paved the way for the development of radiofrequency ablation of BE which has been very successful [4,5], although its utility in squamous dysplasia has not yet been proven.

Not only are there are no RCTs of PDT for esophageal cancer, but there no large prospective cohort studies either. Retrospective cohorts simply give us an indication of areas where better quality studies should be undertaken. The trial published in this edition of the journal is a retrospective analysis of patients who underwent salvage PDT after failed primary treatment with chemoradiotherapy. The work offers some hope, although rather limited in scope. The treatment led to response in 58% and long term survival in 35%, particularly in those who had T1 or T2 recurrence only. If recurrence was more advanced, the treatment did not work.

These findings support and extend previously published retrospective work by others. In one case series 5-year disease-specific survival was 72% in 56 patients treated with PDT as monotherapy, and in another of 21 patients, mean local progression-free survival was 60 months. In a case series of 38 patients, nine of whom received repeat PDT sessions, mean disease-free survival was 32 months and in another, 54% (13/24) of patients were alive without recurrence at a mean follow-up of 21 months [6]. So it does appear that PDT treatment may hold some promise for appropriately selected patients.

Safety Concerns

Apart from PDT induced skin photosensitivity, there is the well known risk of esophageal strictures. Some of these can be very difficult to treat, requiring repeated endoscopic dilatations. But what happens when a T3 or T4 tumor which is invading through the entire thickness of the esophageal wall is treated? Radiotherapy, which requires repeated dosing over some weeks leads to stricturing. There is plenty of evidence that PDT does not affect the collagen scaffold that is important in maintaining the integrity of hollow organs. But in full thickness tumors, the scaffold has been destroyed. Single dose PDT will result in rapid destruction of tumor and may lead to esophageal perforation as there is no time for the supporting scaffold to regenerate. This was seen in the 5/113 patients in the Yano study and has been reported by others also at rates of up to 8% [6]. This is not a good selling point for a treatment!

Is there a future for PDT?

There are good quality data for use of PDT in a variety of premalignant diseases such as actinic keratosis in the skin as well as basal cell carcinoma and recently, it has been proposed for non-cancer applications including infection and to accelerate regeneration of injured tissues. We have explored its use for C. *difficile* diarrhea in the laboratory [7]. Phase 2 and 3 RCTs are now underway for cancers of the prostate and lung. But the modality has not been subjected to high quality trials in other promising areas such as treatment of premalignant lesions of the mouth or for palliation of cholangiocarcinoma, where some very compelling early data have been presented [8].

Prolonged skin photosensitivity is a concern for clinicians and patients alike. Newer drugs may have significant advantages over the ones used previously. Drugs with a shorter biological half-life would reduce the duration of skin photosensitivity and might also open the way to repeat treatments. Slower, more controlled, tissue destruction could permit preferential regeneration of normal tissues, thus lowering the risk of perforation, and, if the PDT drug is preferentially taken up in the mucosa, as ALA is, there may be fewer side effects [3]. But there are other benefits to be had. For example, porfimer sodium, is activated at 630nm, in the red part of the visible spectrum. The depth of penetration of light at this wavelength is no more than 1cm. Penetration depth rises with longer wavelengths. It is quite conceivable that some of the newer drugs which are illuminated in the far red end of the visible spectrum, or even in the near infra-red, might be used to successfully target not only the primary tumor in the esophageal wall but also local para-esophageal lymph node

metastases. This would raise the question as to whether this treatment approach could be used instead of esophagectomy.

An even more elegant application would be better targeting using anitbody fragments or other small molecule targeting agents such as nanoparticles. These would not only increase selectivity for cancer cells, but could completely remove the problem of skin photosensitivity as these drugs would be cleared from the bloodstream within minutes. Proof of principle for this approach already exists [9]

So although we have not yet proven the value of this technology in the clinical environment, there is reason to continue research in this field. Photodynamic therapy may yet replace esophagectomy as the primary treatment for locally invasive esophageal cancer.

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