

A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin

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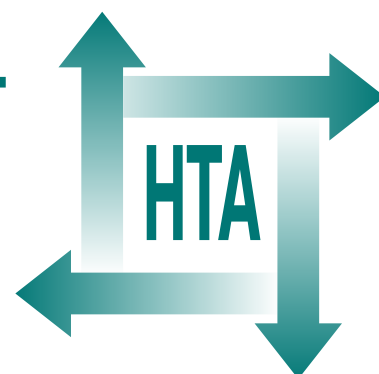
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Executive summary

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Executive summary

Background

Photodynamic therapy (PDT) is the use of a light-sensitive drug (a photosensitiser), in combination with light of a visible wavelength, to destroy target cells (e.g. cancerous or pre-cancerous cells). PDT is generally used either as a primary treatment (usually in skin conditions) or as an adjunctive treatment alongside surgery, radiotherapy or chemotherapy. Although PDT is a fairly well-accepted treatment in clinical practice for some types of skin lesion, as a treatment for other forms of cancer it has yet to be fully explored.

Objectives

The aim of this project was to systematically review the clinical effectiveness and safety of PDT in the treatment of Barrett's oesophagus, pre-cancerous skin conditions and the following cancers: biliary tract, brain, head and neck, lung, oesophageal and skin. The findings will inform decisions about the role of PDT in clinical practice and also the need for further research.

Methods

A comprehensive search strategy was developed to ensure that all relevant sources of data were located. The search strategy comprised the following main elements:

- Searching of electronic databases from their inception was undertaken between August and October 2008; update searches were carried out in a range of electronic databases in May 2009.
- Scrutiny of bibliographies of included studies and existing reviews.
- Hand searching of abstracts from recent relevant conferences.
- Contact with experts in the field and manufacturers of photosensitisers.

Published and unpublished studies from any country, and reported in any language, were eligible for inclusion, provided that they met the following inclusion criteria:

- Study designs: randomised controlled trials (RCTs) in skin conditions and Barrett's oesophagus, non-randomised trials for all other sites.
- Participants: people with Barrett's oesophagus, pre-cancerous skin conditions or primary cancer in the following sites: biliary tract, brain, head and neck, lung, oesophageal and skin.
- Intervention: any type of PDT for either curative or palliative treatment.
- Comparators: any comparator including differing applications of PDT treatments (relevant comparators varied according to the condition).
- Main outcomes: mortality, morbidity, quality of life, adverse events and resource use.

A standardised data extraction form was used. The quality of RCTs and non-randomised controlled studies was assessed using standard checklists adapted as necessary to incorporate topic-specific quality issues. Data extracted from the studies were tabulated and discussed in a narrative synthesis and the influence of study quality on the results of the studies and the findings of the review were discussed. Where appropriate, meta-analysis was used to estimate a summary measure of effect on relevant outcomes with assessment of both clinical and statistical heterogeneity.

Two reviewers independently screened all titles and abstracts, and data extracted and quality assessed the trials. Discrepancies were resolved by discussion or by referral to a third reviewer when necessary.

A scoping review was undertaken alongside the screening stage of the systematic review. The aim of this was to document the extent of the uncontrolled and observational research particularly in those areas for which we anticipated a paucity of controlled trials, thus providing as complete a picture of the evidence base as possible.

Results

The search strategies identified 12,522 references. Full copies of 699 potentially relevant papers were obtained and assessed for inclusion in the systematic review. Duplicate publication of study results and multiple reports of partial data sets appeared to be common. Overall, we included 88 trials reported in 141 publications. Numbers of trials across the conditions studied were: actinic keratosis (AK) (28), Barrett's oesophagus (11), basal cell carcinoma (BCC) (13), biliary tract (5), Bowen's disease (7), brain (2), head and neck cancer (4), lung cancer (7) and oesophageal cancer (13). Some trials covered more than one condition.

There was generally a paucity of well-conducted, adequately powered RCTs. Quality of life and resource outcomes were under-reported. We also identified problems with reporting of key study features and quality parameters, which made the reliability of a number of studies uncertain. Methodological limitations and gaps in the evidence base made drawing of firm conclusions a challenge across the cancer sites and conditions that were investigated. What we were able to conclude was that, overall, PDT appeared to be a promising treatment in the majority of conditions we reviewed. However, the potential place of PDT amongst the range of other treatments available for each condition is not yet clearly defined. Optimal parameters for PDT were unclear in the majority of the areas under investigation.

In actinic keratosis, the only clear evidence of effectiveness was that PDT appeared to be superior to placebo. Uncertainties still exist around PDT's effectiveness compared with other topical treatments. For Bowen's disease there were suggestions of better outcomes with PDT when compared with cryotherapy or fluorouracil but these need further investigation. For superficial BCC, PDT may result in similar lesion response rates to surgery or cryotherapy with better cosmetic outcomes; however, these conclusions are tentative. PDT appeared to be superior to placebo for nodular lesions – less effective in lesion clearance than surgery although with suggestions of better cosmetic outcome. For the treatment of Barrett's oesophagus, PDT in addition to omeprazole appeared to be more effective than omeprazole alone at long-term ablation of high-grade dysplasia (HGD) and slowing or preventing progression to cancer. The priority for PDT research in the area of Barrett's oesophagus is to determine more clearly the role of PDT and its optimal delivery to patients

with HGD. Trials have been conducted with both curative and palliative intent in oesophageal cancer; however, firm conclusions in regard to effectiveness compared with other treatments cannot yet be drawn. No trials were located for early lung cancer, therefore all included trials related to PDT that was used with palliative intent. Further research is needed to determine the role of PDT in relation to current comparators in lung cancer and to identify particular subgroups that might benefit from PDT. In cholangiocarcinoma, PDT may improve survival when compared with stenting alone, and an ongoing trial should provide more definitive evidence. There was very limited evidence on PDT for brain cancer and no definitive statements can be made at present. There was a lack of good trial evidence for cancers of the head and neck, and so the value of PDT compared with other forms of treatment was not clear.

A wide variety of photosensitisers were used across the sites included in this review; these were administered topically or systemically, as appropriate. Overall, there were no serious AEs (SAEs), linked to PDT, reported in these trials. Where the photosensitiser was administered topically for the treatment of skin conditions, local AEs (including pain) ranging in severity were common but largely transient. Systemic administration of meta-(tetrahydroxyphenyl) chlorine (mTHPC) appeared to cause burning sensations at the site of injection, and oral administration of aminolevulinic acid (ALA) was linked to nausea and vomiting. Photosensitisation appeared to have been a problem only in patients receiving the photosensitiser systemically, who did not comply with the recommended precautions against light exposure. The reported data did not permit a comprehensive comparison of the AE profile for each photosensitiser.

Conclusions

Implications for practice

- Photodynamic therapy is currently most accepted in the treatment of malignant and pre-malignant non-melanoma skin lesions. In this review we found evidence of effectiveness for the treatment of AK and nodular BCC in relation to placebo. However, we do not yet fully know the effectiveness of PDT in relation to other treatments.
- The evidence suggested that PDT might be a useful option in the treatment of Barrett's

oesophagus but, again, its effectiveness in relation to other treatments is not yet apparent.

- The evidence for the other sites and conditions examined in this review was not sufficiently clear to draw firm conclusions.
- We did not find any clear evidence implying that PDT should definitely not be used for certain clinical conditions; rather there are a number of uncertainties that require further investigation.

Research recommendations

- The optimal parameters of PDT need to be identified across the conditions studied.
- High-quality trials are needed to compare PDT with relevant comparators for all meaningful outcomes, including quality of life and AEs. Such trials should aim to establish the place of PDT for the treatment of a given condition and should identify if subgroups of patients might respond differently to PDT.
- Good-quality research is needed on the patient experience of PDT across the conditions investigated.

- While the difficulties of conducting high-quality trials in rarer cancers – such as those of the brain and head and neck – are recognised, there is a need to establish where barriers are insurmountable. If RCTs cannot be conducted, other types of evidence may be considered.
- Photodynamic therapy is an active field of research and, as the results of ongoing trials become available, there will be a need to update this review.
- Future work should focus on the cost-effectiveness of PDT in those areas where effectiveness and safety have been established.

Publication

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Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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