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Review Article

Ethical Principles Relevant to the Use of Aspirin as a Treatment of Cancer

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Abstract

There are four basic ethical principles in clinical practice: non-maleficence; beneficence; autonomy and justice. Evidence upon which each of these is judged comes from appropriate research, but there are also personal opinions and claims – many of which are supported by little, if any, research evidence. The evaluation of evidence is likely to be assessed differently by the different operatives involved in any clinical issue: pharmacologists, pharmacists, clinicians, oncologists, research workers, patients and their careers.

In the case of aspirin as a possible treatment of cancer, there are three possible beneficial outcomes to be considered: a reduction in thromboembolism; a reduction in metastatic spread and a reduction in cancer mortality. The main risk is an increase in gastrointestinal and cerebral bleeding associated with aspirin use. This paper attempts to summarise the evidence from research on these risks and benefits.

Keywords: Cancer, Aspirin, Vascular Disease, ASCOLT, Pharmacologists

Non-Maleficence

The first ethical principle in clinical practice is: does no harm. The main harm of aspirin is additional bleeding, in particular gastro-intestinal (GI), and also bleeding from a cerebral vessel. It is most unfortunate that the web carries numerous unsupported statements of opinion, together with the results of studies of patients taking aspirin but with no control patients not on aspirin leading to exaggerated and alarming claims of large numbers of deaths from aspirin [1]. Furthermore, most reports refer simply to the frequency of bleeds, with no attempt to estimate the severity of bleeding truly attributable to aspirin.

Valid estimates of bleeding attributable to aspirin only come from randomised trials and should take account of severity as well as frequency. We decided to base an estimate of the severity upon the proportion of bleeds that led to death, and we therefore conducted a systematic search of the literature to identify large randomised trials in which both total and fatal gastrointestinal bleeds had been recorded. Our search identified 11 suitable trials, based upon a total of 107,000 patients followed for an average of 2.8 years [2].

A meta-analysis of the data from these showed that aspirin is associated with an additional three GI bleeds, or one bleed per 1,000 subjects per year (see table below). The data also show that, using the proportion of bleeds that were fatal as an estimate of the severity of the bleeds that the proportion of bleeds that were fatal in patients taking aspirin was half that of patients who had not been randomised to aspirin. Finally, the bottom line of the table shows that there was no excess risk of a fatal bleed in patients randomised to take aspirin.

Occurrence of a stomach bleed		
- in 52,583 subjects randomised to placebo - in 54,,625 subjects randomised to aspirin	5 per1,000 8 per 1,000	**Risk ratio 1.55** (1.32, 1.83)
Proportion of bleeds that were fatal		
- in subjects on placebo - in subjects on aspirin	8% 4%	Risk ratio 0.50 (0.25, 0.80)
Risk of a fatal bleed in trial participants		
- randomised to placebo - randomised to aspirin	4.7/10,000 3.7/10,000	Risk ratio 0.77 (0.41, 1.43)

Table I: Stomach bleeding in a meta-analysis of data from 11 trials in which aspirin had been randomised for an average of 2.8 years [2].

This conclusion on the safety of aspirin is supported by other published studies[2] and by a recommendation by NICE (The UK National Institute for Health and care excellence) for aspirin as a treatment for some patients at risk of cancer [3].

Intracerebral bleeding is a most serious, but rare event and aspirin is associated with about one such bleed per year in every 1,000 patients. The main factor in cerebral bleeding is blood pressure, and there is evidence from a large randomised trial of aspirin that optimal treatment of hypertension (if present), prevents cerebral bleeding attributable to aspirin [4].

Beneficence

This, the second most important ethical principle of relevance to clinical intervention with aspirin, must be considered in relation to the three possible clinical benefits from aspirin: a reduction in thromboembolism, a reduction in metastatic spread and a reduction in cancer deaths. Furthermore, account should be taken of the effects of aspirin upon the biological mechanisms relevant to each outcome.

Fifty years ago, the first randomised controlled trial showing a reduction in vascular disease mortality by aspirin was reported, and this association has since been repeatedly confirmed [5]. A three-fold increase in vascular disease events in patients with cancer has been reported, and a study in the USA reported that the cause of death in 11% of patients with cancer had been certified to have been from vascular disease [6, 7].

Evidence from clinical studies shows that low-dose aspirin (75-300 mg daily) delays the development of metastases. For example, an overview of five randomised controlled trials of aspirin with over seventeen thousand participants, aspirin was associated with a reduction of about one third in the number of patients who developed metastatic cancer spread. Metastatic spread is of considerable importance because the 'satellite' growths are responsible for much of the pain and the complications of cancer, and many of the deaths are attributable to the metastatic growths, rather than to the primary tumour itself [8-10].

On aspirin and cancer mortality: aspirin has been shown to beneficially affect a large number of biological mechanisms relevant to cancer development and cancer deaths, and these effects give a reasonable basis for an expectation of benefit in cancer [11].This led The Royal Society, in a commentary entitled 'Aspirin; the wonder drug against cancer?' to describe a 'harmony' between the effects of aspirin on biological mechanisms and its effects upon the clinical outcomes of cancer [12].

A wealth of evidence on aspirin and cancer mortality comes from observational studies of survival in cohorts of cancer patients, and some of the cohorts include patients with a wide range of different cancers. In a report based on long-term follow-up of participants in 51 vascular randomised trials, Rothwell et al commented on a reduction in cancer mortality in patients who had previously been randomised to aspirin [13].

In Cardiff repeated systematic searches of the medical literature identified a total of 117 published observational cohort studies, covering a total of almost 1M patients who had, between them, eighteen different cancers. About a quarter of the patients had reported taking aspirin at the time cancer had been diagnosed [14]. Compared with patients who had not taken aspirin, a pooled estimate of the average risk of death from cancer in the patients taking aspirin was about 20% lower (Hazard Ratio (HR) 0.77 Confidence limits 0.72, 0.83).

Most of the 117 cohorts in this study had focused upon the three most common cancers (colon, breast and prostate) but of special interest are twenty-three cohorts of patients with other, less common cancers. In these, aspirin taking was associated with an average reduction of about 21% in cancer deaths – almost identical to the reduction with aspirin in 52 cohorts of the three common cancers (20%) [14]. This last indicates that benefit from aspirin is likely in a very wide range of cancers.

Ten of the cohort studies of patients with cancer in this study also provided data on the duration of survival of the patients [14]. Unfortunately, the measures of survival are so varied that no average estimate of additional survival with aspirin can be estimated. However, all ten cohorts showed an additional survival with aspirin from about three months to five years [14].

In a completely different approach to survival, a group in Liverpool extracted extensive baseline data, including aspirin taking, from the records for 44,000 patients with colon cancer [15]. With these data they constructed a formula giving predicted estimates of survival or death. Entering into the formula the details for a typical non-diabetic patient aged 70 with colon cancer, the inclusion of aspirin taking increases the estimate of survival by about five years for a man, and about four years for a woman.

At the same time, confirmatory evidence on mortality from randomised trials is both seriously limited and inconsistent [16]. While the results of a few opportunistic randomised trials are consistent with a reduction in cancer deaths, randomised trials which have been conducted specifically to test aspirin and cancer mortality have failed to yield evidence of a reduction in mortality at an acceptable level of significance. Thus: the ABC trial in advanced breast cancer was stopped prematurely because of an increase in breast cancer associated with having been randomised to aspirin and a non-significant reduction of only 9% in disease free survival associated with aspirin has been reported recently for the randomised trial, ASCOLT [17, 18].

Based on these last, many argue that judgement on aspirin should be withheld, and recommendations delayed until further adequately powered randomised trials have been completed. At the same time, one cannot but wonder how many trials, in how many different cancers will be required to settle the uncertainty [16].

Autonomy

The ethical issue of autonomy concerns the right of a patient to be involved in every aspect of his or her care and treatment. Aspirin is inexpensive and readily available globally, and it is easily taken with none of the highly distressing effects that accompany some cancer therapies. While aspirin should best be considered as a possible adjunct treatment for cancer, yet for those patients who refuse the more aggressive treatments, and for patients for whom palliative care is judged to be appropriate, aspirin should be seriously considered, and patients suitably informed.

Given the relative safety of aspirin; given the likely reduction in metastatic cancer spread; given its associated reduction in thromboembolic complications and given the support by NICE for aspirin use in a subset of cancers,3 and in view of the extensive and exaggerated misinformation about dangers of aspirin on the web and elsewhere, it seems unreasonable for patients with cancer not to be informed of the valid evidence on the risks and possible benefits of low-dose aspirin [3].

In 2010, early in the work of the Welsh Aspirin Group, a challenge was published in the BMJ: "The debate about aspirin has consumed the medical profession for over 30 years, [*now, almost 50 years*!] yet almost no public participation or consultation has occurred" [19].

In response, a three-day far ranging enquiry - a 'Citizens' Jury - under the general title: 'My Health – *whose responsibility?*' was held in Wales with sixteen members of the general public who had no vested interest in the topic [20]. Over several days, the jury listened to a range of (sometimes contradictory) expert evidence, and the evidence of 'experts by experience', and vigorously debated amongst themselves the various issues raised. An immediate outcome of this initiative was a verdict by the sixteen members of the 'jury' that patients and the public should be more actively involved in the evaluation of the outcomes of research, and in the assessment of its relevance to clinical practice and to public health policy…. and to this last the jurors unanimously added the phrase: '***even before there is agreement between doctors.***

In the UK, the NHS Ethical Clinical Guidelines establish that people have a right to be involved in discussion and have a right to make informed decisions about their care. However, the law in the UK goes further and in a 'Landmark Decision' given by the UK supreme court in 2015 it was stated: 'If information is material, doctors should generally disclose it. They should not wait for the patient to ask' [21]. Surely evidence on the possible benefits of aspirin is highly 'material' to patients with cancer and to their carers!

Justice

The ethical principle of justice acknowledges that decisions pertaining to one person, even if this occurs with fully respect of autonomy, cannot be viewed in isolation. The choices we make for one, may impact on the choices we make for others. With respect to healthcare, which is a finite resource, difficult decisions sometimes need to be made to ensure resources be they financial, access to care or professional time are distributed fairly. In the developed world, health economic analysis is often used to guide whether a resource is value for money and provides a net societal benefit. The financial cost of aspirin is negligible, and the side effect profile is not prohibitive to its safe and effective use. We would therefore assert that the principle of justice favours the active promotion of low-dose aspirin across the poorer countries.

Further to all the above, the situation with cancer in the poorer countries is clearly ethically unjust. One in every six deaths worldwide is due to cancer, giving an estimated 9.6 million deaths in 2018, with around 70% of the deaths in low and middle income countries (LMICs) [22, 23].WHO points out that most cancers in the poorer countries are diagnosed at a very late stage, when most treatments are no longer effective – even if treatments were available, which they are not in many countries [24].Against that background the promotion of aspirin could be of enormous benefit globally, and in particular within the LMICs.

Conclusion

A major strength of the case for the promotion of aspirin as a treatment of cancer lies in the consistent evidence from studies of biological mechanisms and from clinical studies – both showing reductions in both the thromboembolic complications of cancer and in metastatic cancer spread. A further strength in the evidence comes from the

many observational studies of the mortality of cancer patients, though a major uncertainty lies in the limited and inconsistent effects of aspirin on mortality in the few and inconsistent trials with random allocation of aspirin. The balance between 'the consistent evidence' and the 'uncertainty' will undoubtedly be judged differently by the groups mentioned at the outset of this paper, namely: pharmacologists; clinicians; oncologists; research workers; patients and their careers.

Finally, our own judgement is: given that aspirin is relatively a very safe drug, inexpensive, readily available, easily taken, and without any of the highly aggressive side effects of some of the cancer treatments, it is only fair and reasonable that knowledge of the true risks and the probable benefits of the drug should be widely publicised amongst cancer patients and their careers, and patients with cancer should be encouraged to raise the topic of aspirin with members of their healthcare team – leading perhaps eventually to the outcome predicted by one oncologist:

'Aspirin is inexpensive and readily available in almost every country. Its promotion could benefit both the affluent and the indigent within developed and under-developed countries, so that a truly global impact could be realised.' Professor John Chia [25].

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