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Selected reports edited by Janet Fricker

Widespread paediatric use of CAM

→ Pediatrics

Many paediatric patients with cancer use complementary and alternative medicine (CAM), according to a systematic review. It is important, conclude the authors of the UK study, that paediatricians be made aware of the extent of CAM use and furthermore encourage open communication with patients and their parents.

The researchers, led by Felicity Bishop from the University of Southampton, in England, set out to investigate the prevalence of CAM use among paediatric cancer patients and the quality of studies undertaken. The study, they said, represents the first comprehensive systematic review to summarise all the available evidence. The team developed a quality assessment tool (QAT) for surveys on CAM use composed of 17 items that assessed the quality of study design, data collection and data analysis on the reported information.

In total the team reviewed 28 studies, 14 of which were conducted in North America, with the remainder coming from the UK, Turkey, Israel, Singapore, Mexico, Taiwan, Denmark, Finland, the Netherlands, Germany, Hungary and Australia. Altogether, the studies surveyed a total of 3526 children from 14 countries, between 1975 and 2005.

Prevalence rates of CAM use found in the studies ranged from 6% to 91%, with 14 of the articles reporting prevalence rates between 20% and 60%. Herbal remedies were the most popular CAM modality (with use ranging from 2% to 48%), followed by diets/nutrition (3%–47%) and faith healing (3%–30%). Other CAMs commonly used included homeopathy (1%–17%), megavitamins (2%–19%), mind body therapies (9%–27%) and massage therapies (2%–17%).

Results showed that quality of the studies was mixed, with QAT scores ranging from 19% to 79%. Half the studies attained less than 50% of the maximum QAT score.

Altogether, 14 of the articles reported reasons for the children's CAM use, including to help cure or fight the child's cancer and to provide symptom relief from the cancer itself and from the side-effects of standard treatment. CAM use did not appear to be associated with the gender, age, ethnicity or family income of the paediatric patients, indicating wide use across all demographic groups. It did, however, appear to be more common in families with higher parental education.

"Additional research is warranted to better understand this behaviour [CAM use] and to determine and address any needs for patient support and education on CAM use," write the authors, adding that research should prioritise the cost-effectiveness and safety of the modalities.

"Pediatric oncologists need to be aware that their patients (and patients' parents) will be seeking and integrating other therapeutic approaches while undergoing conventional treatments," write the authors.

Limitations of the studies included lack of standardisation of sociodemographic details and definitions of CAM use. Osteopathy, for instance, is considered to be a CAM in the UK, but not in the US. The authors suggest that the use of a generally agreed-on definition of CAM, such as that provided by the NCCAM, alongside a standardised questionnaire would help

achieve the collection of consistent data across different settings.

■ F Bishop, P Prescott, Y Chan et al. Prevalence of complementary medicine use in pediatric cancer: a systematic review. *Pediatrics* 21 April 2010, 125:768–776

Deaths relating to gastric cancer reduced with more extensive lymph node removal

➜ Lancet Oncology

D2 extended lymphadenectomy delivers better locoregional control and cancer-specific survival than limited D1 surgery in patients with advanced gastric adenocarcinoma, concludes the 15-year follow-up results of the Dutch Gastric Cancer Trial (DGCT). The D2 procedure was, however, found to be associated with significantly higher postoperative mortality, morbidity and reoperation rates.

The extent of lymphadenectomy for curative resections in patients with gastric cancer has been under debate for several decades. For the DGCT trial, Ilfet Songun and colleagues from Leiden University Medical Centre, in the Netherlands, set out to assess the effect of D2 compared with D1 surgery on disease recurrence and survival in patients with resectable primary adenocarcinoma of the stomach. In all, 711 patients from 80 participating hospitals were randomly assigned (by means of a telephone call to the central data centre of the trial) between August 1989 and July 1993 to D1 dissection (n=380) or D2 dissection (n=331). D1 dissection entailed removal of the involved part of the stomach or the entire stomach including the perigastric lymph nodes (N1 level, station numbers 1–6) and the greater and lesser omenta. In D2 dissections, both the N1 and N2 lymph nodes (station numbers 7–11) were removed along with the omental bursa and the front leaf of the transverse mesocolon.

Of note is the fact that, at the time of trial, resection of the spleen and pancreatic tail were regarded as necessary for adequate removal of D2 lymph-node stations 10 and 11 in proximal tumours. Today, however, surgery for gastric cancer can be done with a spleen-preserving and pancreas-preserving D2 resection technique, unless removal is indicated because of tumour invasion into these organs.

The five-year results of the study, published in 1999 in the *New England Journal of Medicine*, showed no significant survival benefit in the D2 group, and a higher postoperative morbidity and mortality. However, the 11-year follow-up data, published in 2004 in the *Journal of Clinical Oncology*, showed better survival results in exploratory analyses in patients with stage II and IIIa disease who underwent D2 in comparison with D1 resections.

The results of the current study show that the overall 15-year survival was 21% (82 patients) for the D1 group, versus 29% (92 patients) for the D2 group (P=0.34). The gastric cancer related death rate was significantly higher for the D1 group (48%) compared to the D2 group (37%) (HR 0.74, P=0.01), whereas death due to other diseases was similar for both groups. Local recurrence was 22% in the D1 group versus 12% in D2, while regional recurrence was 19% in D1 versus 13% in D2.

Patients who had the D2 procedure had significantly higher operative mortality rates than those who had the D1 procedure (P=0.004), higher complication rates (P<0.0001) and higher re-operation rates (P=0.00016). Further results showed that patients older than 70 had significantly lower overall survival in both the D1 and D2 treatment groups, male patients had lower survival than female patients in the D2 group (P<0.001) and patients undergoing splenectomy and pancreatectomy had significantly lower overall survival in both D1 and D2.

"Considering that a safer, spleen-preserving D2 resection is currently available in high-volume centres, and our findings of better recurrence and gastric-cancer-related survival rates, D2 resection now seems likely to be the recommended approach for patients with resectable (curable) gastric cancer," conclude the authors.

Commenting on the subgroup analyses, they add, "In selecting patients with gastric cancer for surgery, we do not think that elderly patients should be denied surgery. However, we cannot advocate extensive surgery, especially in elderly male compared with female patients."

In an accompanying commentary, Kevin Roggin, Josh Hemmerich and Mitchell Posner, from the University of Chicago Medical Center, write, "Further debate on the absolute value of extended lymphadenectomy will likely detract from a needed emphasis on defining the optimum timing, choice of drugs and ordering of chemotherapies in patients with gastric cancer."

The authors go on to highlight inconsistencies in the studies, and question why the study did not show differences in gastric cancer deaths until several years after the procedures. "If we assumed that most of these recurrences were secondary to metastatic nodal disease that was not resected with D1 lymphadenectomy, why would the disease remain clinically quiescent for several years in the absence of adjuvant chemotherapy?"

■ I Songun, H Putter, E Meershoek-Klein Kranenbarg et al. Surgical treatment of gastric cancer: 15 year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncology* 20 April 2010, 11:439–449

■ KK Roggin, J Hemmerich, MC Posner. Extended follow-up after extended lymphadenectomy for gastric cancer: was it worth the wait? *ibid* pp 404–405

UK GPs overlook older women with suspected ovarian cancer

➜ British Journal of Cancer

Family doctors appear to be less likely to recognise and refer older women with suspected ovarian cancer for investigations as quickly as younger patients, concludes a UK study. The findings, suggest the authors, may partly explain the UK's poor cancer mortality rates for older people.

Recent studies have suggested that older patients in the UK are not benefiting as much from improvements in cancer treatments as younger counterparts. Rosemary Tate and

colleagues, from Brighton and Sussex Medical School, decided to investigate whether this might partly be due to differential rates of referral, using ovarian cancer as an example.

Studying the General Practice Research Database (GPRD), the investigators identified all women aged between 40 and 80 years on 1 June 2002 with a "Read code" for ovarian cancer recorded between June 2002 and May 2007. Using these records, the investigators compared the GPRD incidence of ovarian cancer with rates compiled from UK cancer registries and investigated the relationship between age and coded investigations for suspected ovarian cancer.

Of the 1107 cases registered on the GPRD over this period, 73% had been coded as having at least one relevant investigation or referral to a gynaecologist in the year before diagnosis. The proportion decreased with age – results showed that 82% of under-55s had undergone at least one investigation in the 12 months prior to diagnosis, in comparison to 75% of 55-to 69-year-olds and 66% of people aged over 70 years.

The researchers also found that GPs were slower to refer elderly women. Women aged 45–69 were typically referred within 10 weeks of visiting their GP, while those aged between 75 and 79 years usually waited for 20 weeks before seeing a specialist.

The rates of recorded diagnoses of ovarian cancer in the GPRD, the researchers found, were lower than those recorded in UK cancer registries for all age groups. However, these differences were much larger for patients aged over 60. For example, for women aged 45–50 the difference was only 5% as compared with 22% for those aged between 75 and 80.

"This study, based on recent information from GP surgeries, suggests that there is a decline in recorded investigation and referral in older women for ovarian cancer," conclude the authors. "Such delays could be an important cause of avoidable morbidity and mortality, and if our results are generalisable to other cancers, they could contribute to the lower survival rates and higher mortality rates experienced in the United Kingdom compared with other European countries."

While the investigators could not say whether the results could be generalised to other cancers, they added, "ovarian cancer would seem to be a good example to study as it is one of the most common cancers experienced by older women, and its prognosis is greatly improved if it is diagnosed at an early age."

The researchers stress that while the reasons for the discrepancy between the GP database and the UK cancer registry are not clear, they might be explained in part by how and when the data were recorded. It may be possible that GPs are less motivated to record cancer diagnoses in older people if they have other serious illness. Furthermore recording details of the disease may be deemed to be less important for older people.

The researchers now plan further studies investigating the different strategies used by GPs in different age groups, and exploring whether these findings can be generalised to other cancers.

■ A Tate, A Nicholson, J Cassell et al. Are GPs under-investigating older patients presenting with symptoms of ovarian cancer? Observational study using General Practice Research Database. *Br J Cancer* 2 March 2010, 102:947–951

Chemotherapy improves survival in NSCLC

➔ Lancet

Chemotherapy improves survival for patients with operable non-small-cell lung cancer (NSCLC), a meta analysis of 47 studies from the NSCLC Meta-analyses Collaborative Group has concluded.

The UK and French investigators, led by Sarah Burdett of the Medical Research Council Clinical Trials Unit, in London, set out to assess the effects of adjuvant chemotherapy, with or without postoperative radiotherapy, in patients with NSCLC who had begun treatment on or after 1 January 1965. The group has previously undertaken two meta-analyses. The first, published in 1995, suggested that chemotherapy with cisplatin-based regimens delivered a 5% improvement in five-year survival that was not statistically significant (HR 0.87, *P*=0.08); while the second meta-analysis, published in 2008, (which included only trials with modern cisplatin-based regimens) found a significant survival benefit of 5.4% (HR 0.89, *P*=0.005). Unlike the group's previous meta-analyses, the current analysis was restricted to patients with early-stage disease.

"In these meta-analyses, we have an opportunity to bring together most trials undertaken during the past few decades, and to assess the effectiveness of adjuvant chemotherapy in patients with non-small-cell lung cancer world wide," write the authors.

The investigators included trials (not confounded by additional therapeutic differences) comparing surgery plus adjuvant chemotherapy versus surgery alone, or surgery plus adjuvant radiotherapy and chemotherapy versus surgery plus adjuvant radiotherapy. The primary endpoint was overall survival, defined as time from randomisation until death from any cause.

The comparison of treatment with surgery alone to treatment with surgery and chemotherapy was made using information from 34 trial comparisons (8445 patients and 3323 deaths). Results showed the addition of chemotherapy provided a 4% absolute increase in survival at five years, from 60% to 64%.

The comparison of treatment with surgery and radiation to treatment with surgery, radiation and chemotherapy included information from 13 trial comparisons (2660 patients,1909 deaths). Results also showed a 4% absolute increase in survival at five years from the addition of chemotherapy, from 29% to 33%.

Subgroup analyses did not show any statistically significant effect of age, sex, histology, performance status, stage or type of chemotherapy on survival benefit. The authors, however, point out that the subgroup analyses contained only small numbers, delivering too low statistical power to detect clinically meaningful differences.

"Our results show a benefit of adjuvant chemotherapy after surgery, which has been already shown in some large trials but not in others," write the authors, adding that although

the absolute survival improvements of 4% at five years are fairly modest, they might result in 10,000 more patients being alive at five years.

In an accompanying editorial, Gregory Kalemkerian, from the University of Michigan, in Ann Arbor, writes, "Because adjuvant chemotherapy has already gained acceptance, the results of these meta analyses add little to clinical practice. Although the studies do offer insight into some unresolved questions, they lack power to provide definitive answers."

He added that adjuvant platinum-based chemotherapy can be recommended for patients who have complete resection of stage II-III NSCLC and have uncomplicated recovery with good performance status within three months of surgery. "Treatment can be considered for patients with larger tumours (T2b, T3) without lymph-node involvement. The scarcity of data means adjuvant treatment cannot be recommended for patients with stage IA." Future studies, he stressed, should focus on the role of adjuvant therapy in patients with IA disease and those aged older than 70 years, and the use of biomarkers to select those who would benefit from specific treatments.

■ NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 24 March 2010, 375:1267–1277

■ G Kalemkerian. Adjuvant therapy for non-small-cell lung cancer. *ibid* pp 1230–1231

Dutasteride cuts prostate cancer risk but delivers questionable clinical benefit

➜ New England Journal of Medicine

Dutasteride reduces the risk of prostate cancer in men at high risk for the malignancy, results from the REDUCE trial have found. But in an accompanying editorial, Patrick Walsh from John Hopkins University, in Baltimore, Maryland, stressed that dutasteride only reduced the risk of low-grade tumours, considered unlikely to be of clinical significance, and appeared not to affect aggressive high-grade tumours, considered more likely to be lethal.

Testosterone, the major circulating androgen in men, is converted to the intracellular androgen, dihydrotestosterone, by steroid 5α-reductase isoenzymes, designated as type 1 and type 2. Dihydrotestosterone is known to drive benign prostate growth and the development of prostate cancer, leading to a move for treatments to target it. Finasteride inhibits the type 2 isoenzyme, while dutasteride inhibits both isoenzymes. Results of the Prostate Cancer Prevention Trial (published in the *New England Journal of Medicine* in 2003), which evaluated finasteride in men with no increased risk of the disease showed that, compared with placebo, finasteride reduced the risk of prostate cancer by 25%, but among the tumours that were detected, there was a 27% increase in the number with Gleason scores of 7–10.

In the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, conducted at 250 sites in 42 countries, Gerald Andriole and colleagues, from Washington University (St Louis, Missouri), report on the effect of dutasteride in reducing the risk of prostate cancer. The trial included 8231 men, aged between 50 and 75, who had an increased risk of prostate cancer as reflected by an elevated PSA level, but no evidence of cancer on biopsies performed within six months of enrolling in the trial. They were randomised to receive a 0.5 mg daily dose of dutasteride or placebo, and underwent a 10-core transrectal ultrasound-guided biopsy at two and four years.

Results at four years show that 659 of the 3305 men (19.9%) taking dutasteride were diagnosed with prostate cancer compared to 858 of 3424 men (25.1%) taking placebo ($P<0.001$). Dutasteride, it was calculated, was associated with a relative risk reduction of 22.8% (95% CI 15.2–29.8, $P<0.001$). Among men with a family history of prostate cancer, the drug reduced the relative risk of a prostate cancer diagnosis by 31.4%. None of the men in the study died of prostate cancer.

Of particular note are results showing that during year 3 and 4 there were 12 tumours with a Gleason score of 8–10 in the dutasteride group, as compared with only 1 in the placebo group ($P=0.003$).

The drug was associated with an unexpected rise in the composite endpoint of cardiac failure, which included heart failure, ventricular failure, cardiopulmonary failure and congestive cardiomyopathy. However, no significant differences were found between the two groups in terms of the rates of cardiovascular events or cardiovascular mortality.

"Among men at increased risk for prostate cancer and for benign prostatic hyperplasia, dutasteride reduced the risk of prostate cancers and precursor lesions and improved many outcomes related to benign prostatic hyperplasia," concluded the authors, adding that dutasteride may be considered as a treatment option for men at increased risk for prostate cancer.

In the commentary, Walsh pointed out that the reduction in the rate of incident cancer was limited to the incidence of prostate tumours with Gleason scores of 5 to 6 (which are moderately well differentiated), and there was no significant reduction in the incidence of tumours that were less differentiated (Gleason scores of 7 to 10), which are considered more likely to be lethal.

"Dutasteride and finasteride do not prevent prostate cancer but merely temporarily shrink tumours that have a low potential for being lethal, and they do not reduce the risk of a positive biopsy in patients who have an elevated PSA level or an abnormal digital rectal examination," wrote Walsh.

Furthermore, he added, introducing these drugs for prevention may be risky. "Because PSA levels are suppressed, men may have a false sense of security, and if prostate cancer ever develops, the diagnosis may be delayed until they have high-grade disease that may be difficult to cure."

■ GL Andriole, DG Bostwick, OW Brawley et al. Effect of dutasteride on the risk of prostate cancer. *NEJM* 1 April 2010, 363:1192–1202

■ P Walsh. Chemoprevention of prostate cancer. *ibid* pp 1237–1238