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Conference on 'Malnutrition matters'

Symposium 4: Hot topics in parenteral nutrition
A review of the use of glutamine supplementation in the nutritional support of patients undergoing bone-marrow transplantation and traditional cancer therapy

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The relationship between glutamine and malignancy can be traced back to the 1950s and the requirement for glutamine for malignant-cell growth in culture. Later studies demonstrated an association between the rate of proliferation of the malignant cells and glutamine usage. The excessive use of glutamine by malignant cells was seen as an opportunity for the development of a treatment using glutamine analogues, but unfortunately excessive toxicity was observed during clinical studies. In animal models glutamine supplementation, initially thought to increase tumour growth, actually causes tumour regression as a result of improved immune clearance of the tumour and appears to reduce the severity of the side effects of chemo- and radiotherapy. This finding led to human studies in both traditional cancer therapy and bone-marrow transplantation, which are reviewed here. Unfortunately, the majority of the studies performed are small and have poor methodological reporting. There is clinical heterogeneity in terms of routes of administration, dosing schedules, chemotherapy regimens and diseases. Studies of glutamine in non-bone-marrow transplantation chemo- and/or radiotherapy treatment suggest a possible trend towards reductions in objective mucositis but no effect on subjective symptoms. There is no evidence for its effect on other clinical outcomes. For bone-marrow transplantation there appears to be some benefit from oral glutamine in reducing mucositis and graft *v*. host disease, while intravenous glutamine may reduce infections but at the expense of an increased relapse rate. Good-quality studies are required in this area.

Glutamine: Cancer: Malignancy: Chemotherapy: Complications

Starting in the test tube . . .

The 1950s brought great advances in cell-culture techniques such that mammalian cells could be continuously grown outside the body. The first immortal cell line used cervical cancer cells (HeLa cells)[1] and much work was done in finding the best culture mediums that allowed maximal cell growth. One nutrient that was found to be important and used avidly by the tumour cells was glutamine[2]. Scientists, now aware of a relationship between cancer and glutamine, investigated matters further.

It became apparent that the more rapidly growing, hence more aggressive, the tumour the more glutamine it metabolised[3]. Animal studies raised the possibility of a 'glutamine trap' in which the tumour consumes glutamine at a higher rate than other tissues and deficiency occurs[4]. This deficiency, it was thought, may have led to the cachexia and weight loss of malignancy. However, many of these studies used mouse and rat models of cancer in which the tumour was between 10% and 20% of the body weight of the animal, a much greater percentage than in human malignancies[5].

Glutamine supplementation: good or bad?

In animal models of cancer many researchers had thought that glutamine supplementation would cause increased

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Table 1. Summary of randomised controlled studies of the administration of glutamine to patients receiving chemo- and/or radiotherapy

Study	Glutamine	Cancer	No. of patients	Chemotherapy	Outcomes
Anderson *et al.*[11]	Oral	Soft tissue tumours	24	Various	Mucositis
Cerchietti *et al.*[12]	Intravenous	Head and neck	29	Chemoradiotherapy	Mucositis and infections
Daniele *et al.*[13]	Oral	Bowel	62	5-FU	Mucositis
Decker-Baumann *et al.*[14]	Intravenous	Bowel	24	5-FU	Mucositis
Huang *et al.*[15]	Oral	Head and neck	17	Radiotherapy	Mucositis
Jebb *et al.*[16]	Oral	Bowel	28	5-FU	Mucositis
Okuno *et al.*[17]	Oral	Bowel	134	5-FU	Mucositis
Peterson *et al.*[18]	Oral	Breast	326	Anthracyclines	Mucositis
van Zaanen *et al.*[19]	Intravenous	Haematological	20	Various	Infections and toxicities

5-FU, 5-fluorouracil.

tumour growth, as the amino acid appeared to be an important fuel for the tumour. Supplementation with glutamine actually causes tumour regression in some cases because glutamine is the preferred fuel of the body's tumour-killing cells, the natural killer cells[6].

Glutamine was given to rats and mice after they had received chemo- and/or radiotherapy and it was found to reduce damage to the gut[7,8], hence reducing infections, which are a major cause of morbidity and mortality in patients with cancer.

Human studies

With the encouraging evidence from animal studies of decreased side effects of chemo- and radiotherapy and the suggestion that glutamine does not increase tumour size several studies of glutamine supplementation in human subjects were conducted.

The studies gave either oral or intravenous glutamine and the intravenous glutamine was given either with total parenteral nutrition or alone. The studies can be further divided into those in which patients received bone-marrow transplantation and those in which patients received traditional chemotherapy.

Chemotherapy and radiotherapy

Traditional chemotherapy involves the administration of cytotoxic drugs that kill rapidly-dividing cells, which include malignant cells[9]. After administration there is a rest period during which the body recovers from the chemotherapy before more is given. Chemotherapy also damages rapidly-dividing normal cells, e.g. cells lining the gut, hair follicles and the bone marrow. It is the damage to the normal cells that leads to the side effects (mucositis from gut damage and increased infections from bone-marrow damage)[9]. Radiotherapy is the administration of radiation, usually in the form of ionising radiation, which as in chemotherapy damages rapidly-dividing cells[10].

A brief search of PubMed has revealed nine randomised controlled trials that administered glutamine to patients receiving chemotherapy and/or radiotherapy[11–19]. These studies are summarised in Table 1. Examination of one study[18] led to concerns over the methodology of the study and consequently it will not be discussed further.

Considerable heterogeneity was found in the studies in relation to dosages and routes of administration of glutamine, malignancies and clinical outcomes. Unfortunately, the majority of the studies were small and had poor methodological reporting. Three studies report reduced mucositis with glutamine[11–13], while two report reduced subjective measures of mucositis (gut absorbtive capacity and endoscopic appearances) but no reduction in subjective symptoms of mucositis[14,15]. Three studies report no change in mucositis[16,17,19]. Neither of the two studies reporting infections[12,19] demonstrates a difference in the number of infections.

Meta-analysis (Review Manager version 5.0 software; Cochrane Collaboration, Oxford, UK) was possible in two outcomes, which are reported as risk ratio and 95% CI. No significant difference was found between placebo and control when the presence of mucositis (objective measures risk ratio 0·94 (95% CI 0·65, 1·36) and subjective measures risk ratio 1·40 (95% CI 0·96, 2·05)) or severe mucositis (objective measures risk ratio 0·82 (95% CI 0·57, 1·18) and subjective measures risk ratio 1·12 (95% CI 0·68, 1·84)) was analysed. The forest plots are shown in Figs. 1 and 2.

Bone-marrow transplantation

The dose-limiting factor in giving chemotherapy is bone-marrow toxicity[20]. The harvesting of a patient's bone marrow, storing it while chemotherapy is administered and then re-infusing the marrow after the chemotherapy allows higher doses of chemotherapy to be given (autologous transplantation) as the bone marrow is spared from the effects of the chemotherapy. Using a donor's marrow (allogeneic transplantation) has the added advantage that the transplanted cells attack malignant cells (graft *v.* leukaemia effect) but this procedure can also be detrimental if the graft attacks normal tissues (graft *v.* host disease). Bone-marrow transplantation results in prolonged hospitalisation, infections and mucositis to a greater extent than traditional chemotherapy regimens[20].

A systematic review of glutamine supplementation and bone-marrow transplantation has recently been completed[21]. Briefly, the search has produced seventeen[22–38] randomised controlled trials, of which seven used oral glutamine[22–28] and ten used intravenous glutamine[29–38].

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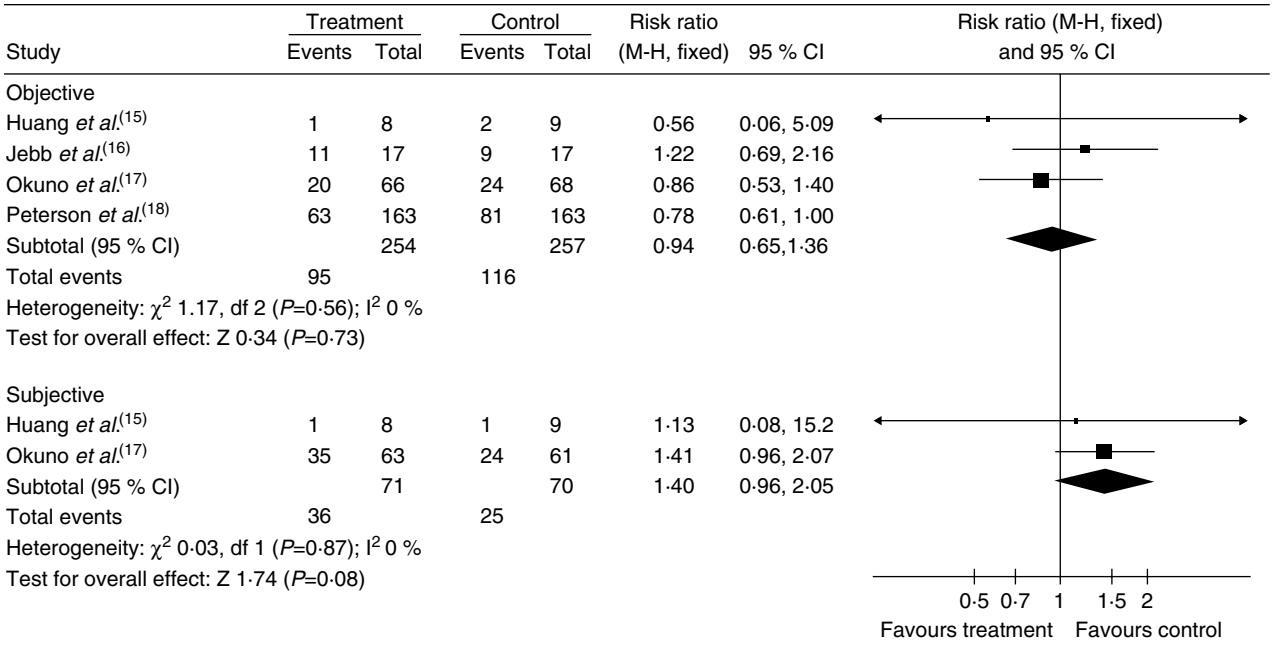

Fig. 1. Meta-analysis of the presence of mucositis in patients undergoing non-bone-marrow transplantation chemo- and/or radiotherapy. M-H, Mantel-Haenszel; ←, →, values extend beyond range of values shown.

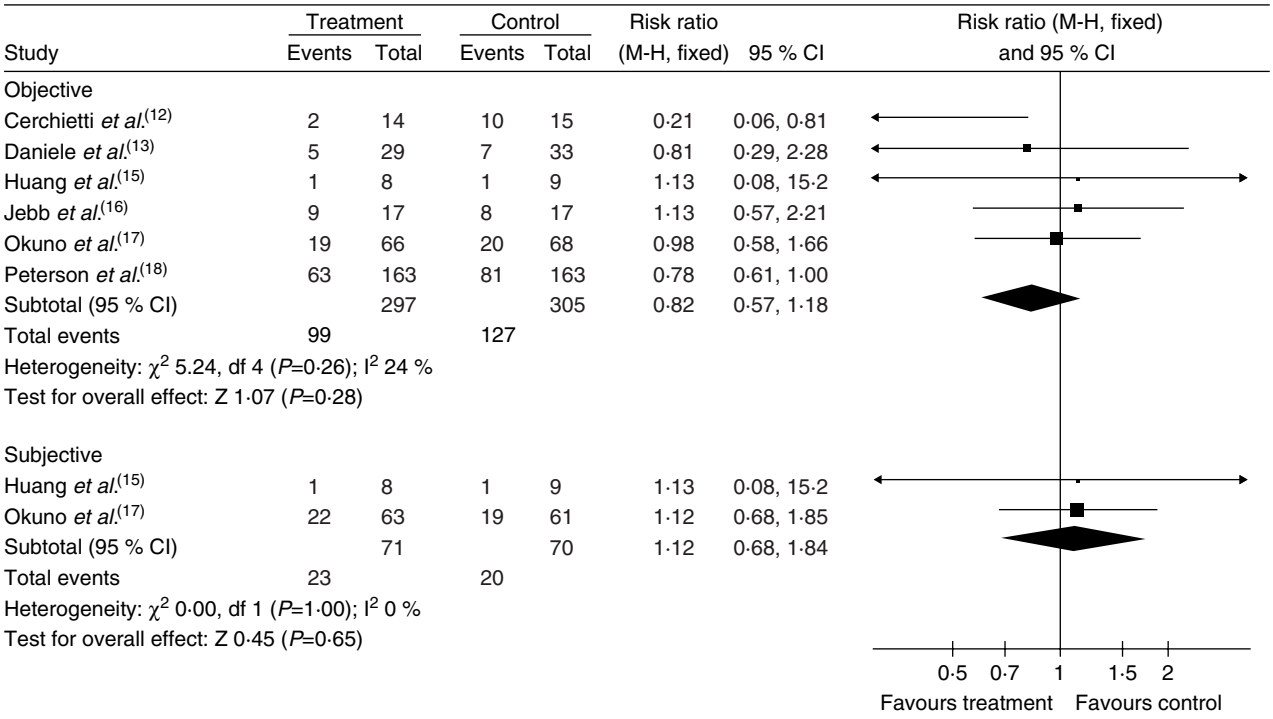

Fig. 2. Meta-analysis of the presence of severe mucositis in patients undergoing non-bone-marrow transplantation chemo- and/or radiotherapy. M-H, Mantel-Haenszel; ←, →, values extend beyond range of values shown.

Five studies investigated autologous transplantation[24,26,30,32,33] while four investigated allogeneic transplantation[27,29,34,38] and seven were mixed transplant types[22,23,25,28,31,35,37]. Considerable heterogeneity was found in ages, dosing and underlying diseases.

Meta-analysis of these studies suggests a decrease in mucositis and graft *v.* host disease with oral glutamine but no effect with intravenous glutamine. There is also a reduction in infections with intravenous glutamine. There is, however, an increase in relapse with intravenous

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glutamine but this result was based on two small studies[30,32] of patients undergoing autologous transplantation.

Conclusions

Glutamine and cancer have a long history but so far there is no clear evidence for glutamine supplementation following conventional chemotherapy. A similar conclusion has been reached by the Cochrane review in this area[39]. The problem has been that the majority of the studies performed have been small and have poor reporting of methodology. There have also been several different regimens of glutamine dosing and administration. The chemotherapy used and the tumours treated have also been different. There may therefore be a benefit in specific cancers and chemotherapy regimens.

There have been a larger number of studies performed with patients undergoing bone-marrow transplantation, but again many of these have been small and demonstrate poor methodological quality. There may be benefit for oral glutamine in reducing mucositis and graft *v*. host disease and for intravenous glutamine in reducing infections, but this outcome may be at the expense of increased relapse.

In both areas larger well-conducted and -reported randomised controlled trials are required.

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