Impact of enteral immunonutrition on infectious complications and immune and inflammatory markers in cancer patients undergoing chemotherapy: a systematic review of randomised controlled trials

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Abstract

Background: There is increasing awareness of the importance of nutritional support in cancer treatment including the interaction with immunity. Immunonutrition is the provision of one or more nutrients (e.g. Vitamins A, D, or E, omega-3 fatty acids, arginine and glutamine) known to modulate immune function when given at levels above those normally encountered in the diet in order to support immune system function or modulate its activity, including control of inflammation. We reviewed the role of oral or enteral immunonutrition versus standard nutrition on infection and infection-related biomarkers in adult cancer patients undergoing chemotherapy.

Methods: A systematic search of oral or enteral immunonutrition versus standard nutrition in adult cancer patients during chemotherapy with or without radiotherapy or haematopoietic stem cell transplant was conducted in MEDLINE, EMBASE and CENTRAL. The search was limited to randomised controlled trials. Our primary outcome was infectious episodes or immune-related biomarkers (e.g. immune cell numbers, inflammatory markers). Secondary outcomes included incidence of malnutrition or cachexia, non-infection related adverse events (AEs), rate of remission, survival, and delays or incomplete cycles of chemotherapy. Risk of bias was assessed using ROB 2.0 and study quality was assessed using CASP for RCTs.

Results: The search yielded seven studies involving 521 patients (261 immunonutrition, 260 control) for analysis. All studies enrolled patients with solid tumours (no haematological malignancies). Studies were heterogenous for cancer type (upper gastrointestinal, head and neck, pancreatic and lung), immunonutrient composition (omega-3 fatty acids, vitamin A, E, glutamine, arginine or nucleotides), delivery route (enteral nutrition or oral nutritional supplement) and control used. Intervention period ranged from 4 to 14 weeks. No study reported absolute number of infections. Three studies reported AEs including potential infectious episodes of febrile neutropenia, pneumonitis and mucositis with oral candidiasis. Some studies report a decrease in blood concentrations of CRP and TNF-α with immunonutrition.

Conclusion: There is currently insufficient evidence to define a role for immunonutrition on infectious episodes during chemotherapy in adult cancer patients. Further well-defined studies that account for

degree of malnutrition, dose, timing and duration of immunonutrition in specific well-defined cancer groups using a standardised outcome framework are needed.

Introduction

Systemic chemotherapy remains a primary treatment for haematological and non-haematological cancers. Despite more targeted treatments and lower dose regimens, systemic chemotherapy is still associated with immunological impairments. Immune, endothelial and epithelial cell damage compromise the immune response. A neutropenic period occurs 10 to 14 days post chemotherapy, for an average of 3 to 4 weeks (1), although duration can vary by individual and treatment. Up to 60% of febrile neutropenia presentations are due to infection (2) with a mortality rate of 2 to 12% (3) which, if untreated, rises to 21% (2).

A compromised nutritional status can also impair immune function and increase infection risk (4) (5). Reported incidence of malnutrition ranges from 20 to 70% depending on the age of the patient, and the type and stage of cancer (6). One French study found that 1 in 3 cancer patients were malnourished, with significantly greater antibiotic use in the malnourished cohort (35.5 *vs* 22.8%; $P<0.001$) (7). Epithelial cell damage during chemotherapy can lead to mucositis, enteritis or colitis, which may exacerbate anorexia, lead to malabsorption and result in worsening malnutrition. Bacterial dysbiosis secondary to prophylactic antibiotic use, chemotherapy enteritis/colitis and malnutrition can also impair immune function (8). Subsequent, infections during chemotherapy can lead to incomplete treatment cycles, increased health care costs and sepsis resulting in death (9).

A range of nutrients have been shown to have immune-modulating effects (10)(11) including but not limited to omega-3 fatty acids (12)(13), arginine (14), glutamine (15)(16), vitamins A (17), C (18), D (19) and E (20), nucleotides (21) and the trace elements zinc (22) and selenium (23)(24). Different combinations of these nutrients have been included in commercial formulas used in the surgical oncology setting (25)(26)(27). These formulas are collectively described as immune-enhancing formulas, immune-modulating formulas or immunonutrition. Thus, immunonutrition is the provision of one or more of these nutrients at levels higher than would normally be encountered in the diet, with the aim of supporting the function of the immune system or modulating its activity, including control of

inflammation (28)(29). The ESPEN guidelines on nutrition in cancer patients refer to arginine, omega-3 fatty acids and nucleotides under the heading “immunonutrition” (27). There is currently no consensus on therapeutic doses for these nutrients regarding their effect on immune cell function or infective episodes, but immunonutrition is discussed in the ESPEN Guidelines on nutrition in cancer patients (27), in surgery (30) and in the intensive care unit (31).

Enteral delivery of nutrition has been recommended over parenteral nutrition (272) due to the association of parenteral nutrition with increased infection risk (32) and impaired glycaemic control (33). A recent meta-analysis exploring the impact of enteral immunonutrition on mucositis in adult patients undergoing chemotherapy showed no improvement in overall incidence of mucositis (relative risk (RR) = 0.91; 95% confidence interval (CI) 0.79, 1.05) (34). However, the analysis did show a reduction in incidence of grade $\geq$3 oral mucositis, diarrhoea, oesophagitis and body weight loss (34).

Provision of immunonutrients either alone or in combination may prove an effective strategy in modulating the adverse immunosuppressive impact of chemotherapy. Despite some evidence of a potential role of immunonutrients in supporting innate and adaptive immune function in the surgical oncology setting, a systematic review of their effect on infectious outcomes in cancer patients during chemotherapy is lacking. This systematic review aims to explore the effect of enteral immunonutrition on infectious events or immune-related biomarkers in adult cancer patients during chemotherapy (with or without radiotherapy).

Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) reporting framework was adhered to (35) and a checklist is provided (supplementary materials A).

Eligibility criteria

We included prospective randomised controlled clinical trials (RCTs) of adults (16 years and older) receiving immune-enhanced oral nutritional supplements (ONS) or enteral nutrition (EN) during chemotherapy with or without radiotherapy in a health care setting. Studies delivering enteral immune-enhanced ONS or EN formulations that included at least one immunonutrient (omega-3 fatty acids,

vitamins A, E, or D, zinc, selenium, arginine or glutamine), with a dietary control (i.e. oral diet, nutrition counselling ± EN or ONS in the absence of an immunonutrient) were included (see Supplementary materials B for search terms used).

Studies delivering immunonutrients parenterally (intravenous (IV) or total parenteral nutrition) or pharmacologically (capsule/tablet) were excluded in order to evaluate the impact of enteral delivery of immune-enhanced ONS or feed, while also removing potential bias of increased infection risk seen during IV procedures. Studies with comparators containing a single immunonutrient versus an intervention of multiple immunonutrients were excluded. Pre or probiotic comparators were excluded and pre and probiotics were also not included as immunonutrients in this review. While it is recognised that pre and probiotics have potential to modulate immune function via alterations to gut microbiota, the high incidence of antibiotic use during chemotherapy and lack of standardisation in microbiota analysis and reporting rendered them out of scope. Non-randomised or retrospective studies were excluded due to a potential risk of bias. Duplicate studies or studies that failed to report patient data (i.e. review articles, letters to editor, case reports and conference abstracts) were excluded. Studies that did not report on an outcome of relevance or had missing data were excluded if attempts to get source data failed.

Types of participants

We included adult patients aged 18 years or older and those teenage and young adult patients (aged 16-17 years) treated in an adult cancer unit with a confirmed cancer diagnosis. Due to the limited literature available for the use of immunonutrition in the chemotherapy setting, a heterogenous search of cancer diagnoses was performed to support identification of greatest potential impact by diagnosis. Patients were treated with chemotherapy with or without radiotherapy, including chemotherapy prior to haematopoietic stem cell transplantation (HSCT) or surgery where end of study outcomes were reported prior to these interventions.

Patients aged 18 years or under treated in a paediatric setting were excluded. Surgery, immunotherapy or HSCT only studies were excluded, due to their independent effect on immune cell function and infection risk. Studies of induction or neoadjuvant chemotherapy where primary outcomes were measured after surgery or HSCT were also excluded.

Types of outcome measures

The primary outcome was the incidence of infection as indicated by clinically reported infectious events (i.e. CTCAE, microbiology or virology reports) or infection-related haematological markers (i.e. C-reactive protein (CRP), cytokines, immune cell numbers (total white blood cell (leukocyte) count, neutrophils, lymphocytes)). Secondary outcomes included incidence of malnutrition (as defined by a validated nutrition screening tool or assessment process (pg-SGA)), non-infection related adverse events (AEs), rate of remission, survival, and delays or incomplete cycles of chemotherapy.

Information Sources and Search Strategy

A comprehensive and systematic search was conducted in MEDLINE (R) ALL (1946 to Daily Update) and EMBASE (1947-present, updated daily) using the OVID platform and the Cochrane Central Register for Controlled trials (CENTRAL). The search was performed on 19th Nov 2020 with an updated search performed on 2nd June 2022.

A subject specific search strategy (immunonutrition, cancer and chemotherapy) was developed in MEDLINE using relevant MeSH headings and combined with a randomised trial optimisation strategy (36) for greatest sensitivity (see supplementary materials B). The search strategy was then optimised for each database and reviewed by a healthcare librarian.

The search was limited to publications in the English language with available full text articles. There were no limits on date of publication. Search results were downloaded into EXCEL (Ver10) and transposed into an agreed study selection template for article management. Reference lists of included studies and relevant reviews were hand searched and any identified studies meeting the inclusion criteria were included.

Selection of studies

Studies were screened independently by two reviewers (CD, LM) for eligibility against study inclusion and exclusion criteria. Reviewers were blinded to results until screening was completed. Full texts from reference lists agreed to be relevant by LM and CD were included. Any disagreements were adjudicated by a third reviewer (PC or FM).

Quality assessment and data extraction

Trial characteristics and study data were collated using a pre-piloted data extraction table; this was done independently by LM and reviewed by CD. Any disagreements were resolved by discussion with a third reviewer (PC or FM). Study characteristics included publication details, population and treatment, intervention (type, mode of delivery, timing, compliance, comparator) and trial outcomes. Authors were contacted for further information on product composition, infectious events and clarification on some reported data, with consent obtained for reporting of previously unpublished data.

Risk of bias and quality assessment

Critical appraisal of the studies followed the three parameters outlined by IOM Standard 3.6 (37). Risk of bias was assessed using the Cochrane Collaborations tool Rob 2.0 (38) on an “intention to treat” basis independently by two reviewers (LM, CD or PC). The domains assessed were: 1. Bias arising from the randomisation process, 2. Bias due to deviations from intended interventions, 3. Bias due to missing outcome data, 4. Bias measurement of the outcome and 5. Bias in selection of the reported result. Each was graded as “low risk”, “some concerns” or “high risk”. Disagreements were discussed and resolved through mutual agreement.

A bias selection graph was produced. Study certainty was assessed using the Critical Appraisal Skills Programme (CASP) of the Public Health Resource Unit (PHRU), UK for randomised controlled trial standard checklist (39) to review study design, methods, results, and interpretation. Reporting of potential confounders (i.e. age, nutritional status, intake and weight loss) was also included.

Data synthesis and analysis

Extracted data are qualitatively and quantitatively described. Interventions are described in terms of their constituents, delivery methods and compliance. Study characteristics and quality scores are summarised and tabulated. A meta-analysis was planned where 2 or more studies of similar homogeneity in terms of intervention composition, cancer diagnosis and comparator arm were identified to enable a clinically relevant analysis (See PROSPERO protocol for detailed analysis plan).

Registration of Systematic Review

The protocol for this systematic review and meta-analysis was registered with the PROSPERO database (https://crd.york.ac.uk/PROSPERO/) with registration number CRD42020223758.

Results

Inclusion of studies

The process for article inclusion or exclusion is reported in an adapted PRISMA flow diagram (Figure 1). The search yielded 4879 articles with 566 duplicates. After abstract and title screening against study inclusion criteria, 23 articles were selected for full paper review with 7 articles (representing 7 studies) meeting the inclusion criteria. No additional studies were identified from reference screening of included articles or from the updated search on 2nd July 2022

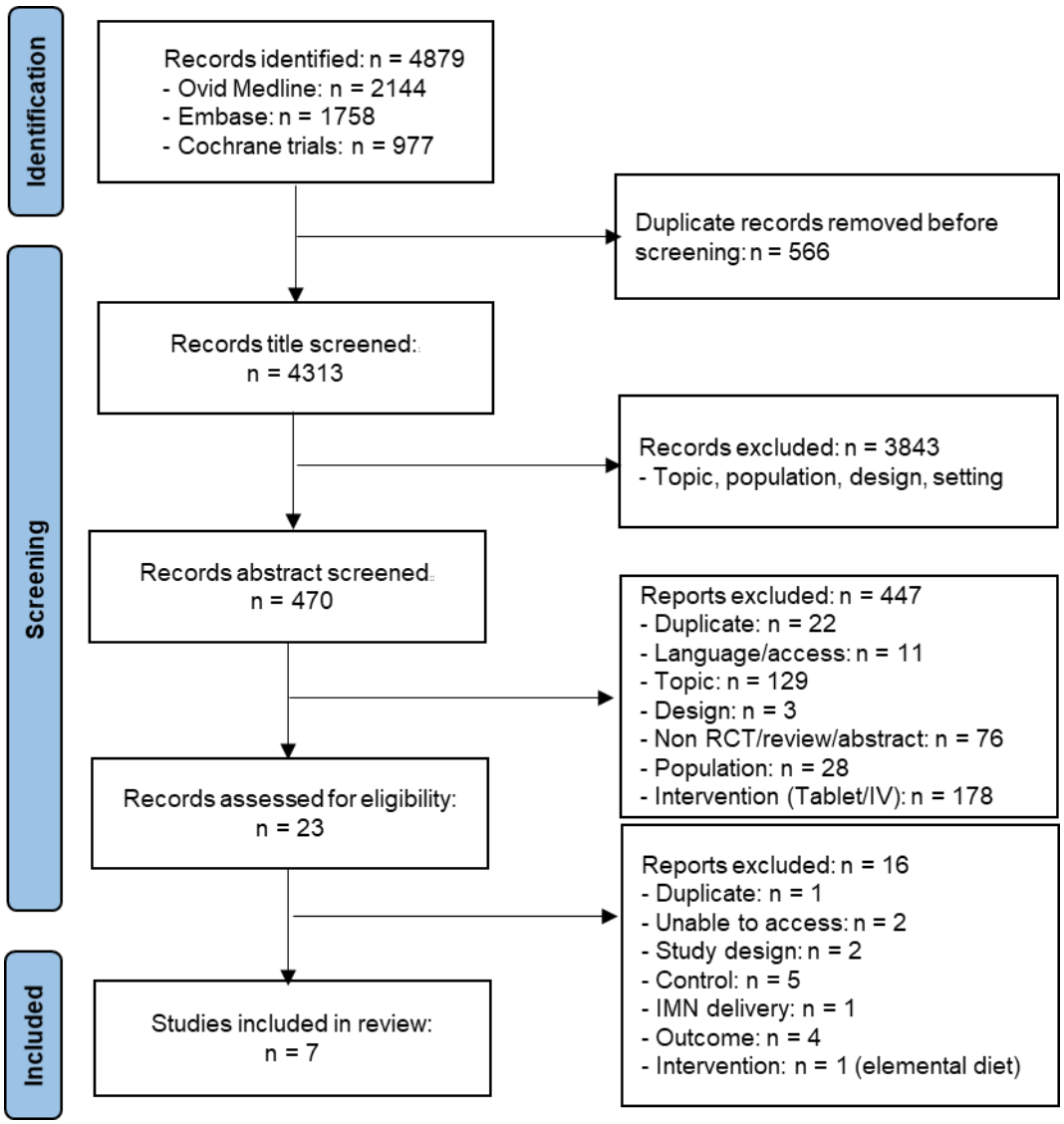
Study characteristics

Seven studies involving 521 patients (261 immunonutrition, 260 control) were identified for inclusion. Detailed study characteristics are described in Table 1. All studies were in patients with solid tumours; there were no identified studies of enteral immunonutrition in patients with haematological malignancies.

Type of cancer varied across studies: four studies were heterogenous (40)(41)(42)(43) and three homogenous (44)(45)(46) for cancer type. Patients were treated with either chemotherapy alone (43)(44) or in combination with radiotherapy (40,41,42,45,46). Only one study was homogenous for chemotherapy alone and cancer type (44).

Differences in baseline characteristics were found in one study, which reported more alcohol drinkers in the immunonutrition compared with the control group (61.8% vs 42.9% p=0.046) (42). Another study neared significance for median age (IQR) with a younger immunonutrition than control group (53 yr (47-60 yr) vs 59 yr (50-64 yr), p=0.06) (40). None of the other studies showed any significant differences in baseline characteristics between groups.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of study inclusion/exclusion



INSERT Table 1: Characteristics of the included studies

Immunonutrient composition

Study immunonutrition formulations varied, as did the delivery method; details on product, composition, dose, and delivery are given in Table 1. Missing information was provided by authors or companies. Two studies used omega-3 fatty acid enriched supplements (Supportan (42) and Forticare (43)). Five studies used products with more than one immunonutrient: Impact (omega-3 fatty acids, arginine and

nucleotides) (41); Neo-mune (omega-3 fatty acids, arginine and glutamine) (40)(46) and ProSure (omega-3 fatty acids, vitamin A and vitamin E) (44)(45). Nutrient composition of these formulas is included in Supplementary Table 1.

Intervention delivery

Intervention period ranged from 4 to 14 weeks. Immunonutrition formulas were delivered either via a tube (Percutaneous Endoscopic Gastrostomy (PEG) or Nasogastric Tube (NGT)) (40)(41)(42)(46) or as an ONS (43)(44); one study used ONS or enteral tube feeding (PEG/NG) depending on cancer type (40). In each study, patients were allowed to eat if able to. Dietary advice was provided in two studies (40)(45); the other studies either didn't report this or only advised on how to take the immune-enhanced ONS.

Three studies used diet only as a control, two with normal diet (40)(45) and one with a standardised calorie-controlled diet to meet requirements (44). Most enteral tube feeding protocols provided a set dose of immunonutrition formula plus an isocaloric $\pm$ isonitrogenous equivalent to meet participants' estimated requirements (40)(41)(42)(46).

Methods used to estimate requirement for total caloric and protein provision were reported in four studies, three using between 30 and 40 kcal/kg/d or 1.5 to 1.8 g protein/kg/d (41)(42)(46) and one a Harris Benedict estimate (44).

Four study designs aimed to calorie match ONS or enteral tube feed provision between the immunonutrition and control groups (41)(42)(43)(46), with two studies providing 500-560 kcal/d more in the immunonutrition group (40)(45). One study provided a standardised calorie-controlled menu for both groups subtracting the caloric provision of the nutritional supplements for the intervention group to support an isocaloric intervention (44). Both groups had similar caloric provision during treatment ($p=0.83$) (44). Protein provision was more varied: one study provided 10 g/d more in the control group (41), while four studies provided between 9 and 31 g/d more with the immunonutrition formula (40)(42)(43)(45). The study utilising a standardised calorie controlled menu to meet nutritional requirements showed similar calorie and protein provision between groups on diary analysis (44).

Sunpaweravong et al. provided a standard feed to all patients before and after the intervention period and delivered isocaloric isonitrogenous matched immunonutrition and control (46).

Intervention compliance

Five studies reported intervention compliance (41)(42)(43)(44)(45); compliance was measured by diaries of ONS intake and returns of unused products. Where compliance was reported, enteral feed provision showed improved delivery of target volumes of immunonutrition (82.7% $\pm$ 17.9) (42) compared to ONS (12.9% to 73%) (43)(44)(45). Compliance appeared to be a particular problem with omega-3 fatty acid fortified products; with reported causes for reduced compliance including gastrointestinal side effects (43) and aversion to product taste (45). Authors did however acknowledge that it was difficult to discern if patients were conflating cancer treatment related side-effects with nutritional supplementation.

One study showed participants who took more than 50% of their prescribed volume (2.2 g EPA) ($p=0.042$) were able to maintain their skeletal muscle mass compared to the losses seen in the control group and those taking less than 50% of their dose (45). In the same study, 54.8% of patients consumed less than half their prescribed volume of immunonutrition with 25.8% consuming none (45). One study inferred compliance via increases in the incorporation of EPA and DHA into leukocytes; with 4.5 x increase in EPA and 2.5 x increase in DHA ($p<0.05$) in the treatment group (41). Between group compliance was measured in two studies and varied dependent on delivery route (42)(43). Delivery of immunonutrition via ONS (28.6% vs 11.8%; $p=0.08$) (43) was less well tolerated than enterally delivered products (82.7% $\pm$ 19.9 vs 76.9% $\pm$ 28.7; $p=0.879$) (42).

Risk of bias

INSERT Figure 2: Risk of Bias

An overview of risk of bias assessment is shown in figure 2. Randomisation was independently ascribed in two studies (41)(42) and adequately described in four studies (40)(43)(44)(45). One study stated randomisation took place, but no details were provided (46).

Stratification was described in four studies and included cancer type (41)(44), recruiting centre (41), diabetes mellitus, inflammatory status and Glasgow Prognostic Score (GPS) (46) while one study documented that stratification took place, but no details were provided (42).

Sample sizes ranged from 28 to 111. Five studies reported power calculations; for one study it was unclear as to the outcome used for estimations (44), two used body composition outcomes (skeletal muscle mass and psoas major muscle area (PMA) (45) and change in body cell mass (BCM) (42)), one mucositis (41) and the other compliance and inflammation (43). Three studies reported they were underpowered (42)(43)(44), one of which was unable to report the primary outcome (mucositis) but did have sufficient power to report the secondary outcomes of immune cell types and function (42). No included studies were powered to assess infectious episodes. There were no reported significant differences in baseline characteristics known to affect immunological status, such as age, sex, and nutritional state (BMI, weight) between groups within any study.

Blinding was described in two studies; one was double blinded with enteral product concealment (43) while the other was single blinded to investigators only (44). We were unable to access protocols for three studies (41)(42)(44) to review adherence to planned analysis and study design. Where protocols were available, detailed analysis plans were often not reported.

There were no reported deviations from intended interventions reported. Greater drop-out in the control arm was reported in two studies (41)(43). All eligible participants were included in the intention-to-treat analysis in all studies. There was no observable bias due to outcome reporting in any study. One study grouped grade ≥3 haematological and non-haematological AEs (40). The differential energy and protein provision between groups and poor compliance to immunonutrition were identified as potential sources of bias.

The effect of immune-enhanced ONS or EN interventions on outcomes

Effect on infectious complications

No studies reported absolute numbers of infections. Three studies reported AEs which included potential infectious episodes, such as febrile neutropenia (40)(45), bacterial pneumonitis (40) and mucositis (40)(46). One study reported that all cases with febrile neutropenia had oral candidiasis (40) and another

didn't report infectious causes (46). A single study reported a significant between group difference in grade 3-4 haematological toxicities with fewer in the immunonutrition group (23% control vs 5% IMN; p=0.03) (40). The same study reported no between group difference (P=0.5) in admissions secondary to AEs (40). In the control group, four patients (head and neck cancer) were admitted with febrile neutropenia (hemoculture negative) and two (oesophageal cancer) with bacterial pneumonitis. In the immunonutrition group, four patients (2 head and neck and 2 oesophageal) were admitted with febrile neutropenia (hemoculture negative) and one (head and neck) with grade 3 mucositis (oral candidiasis) (40).

Effect on immune cell numbers, phenotypes and function

Two studies measured influence of immunonutrition on immune cell numbers (41)(46). One study showed a small non-significant decrease in blood numbers of various immune cell types (CD3, 4, and 8 cells, total white blood cells, polymorphonuclear cells and total lymphocytes) in the immunonutrition vs control group (46). The other study showed immunonutrition helped to maintain the ratio of $CD4^+$ to $CD8^+$ lymphocytes between the start and end of chemoradiotherapy compared to standard nutrition ($p<0.05$) (41). The study also observed an increase in expression of immune cell receptors, antioxidant enzymes, cytokines, inflammatory proteins, NADP(H) oxidase subunits alongside alterations in transcription and transduction factor induction at end of immunonutrition treatment (41). There was also an increase in pro-angiogenic factor (VEGF-alpha) (41).

INSERT Table 2: Inflammatory markers.

Effect on pro-inflammatory markers

CRP was reported in five studies (Table 2a) (41)(43)(44)(45)(46) and TNF-α in four (Table 2b) (41)(42)(44)(46). No studies showed a significant between group difference in CRP or TNF-α at baseline. One study (46) involving arginine, glutamine and fish oil (a source of omega-3 fatty acids) delivered via PEG showed a significant decrease in CRP (p=0.001) and TNF-α (p=0.014) between start and end of treatment. A study of omega-3 fatty acids (34) showed a significant decrease between start and end of treatment CRP (p=0.02) and TNF-α (p=0.05) in the immunonutrition group; this neared significance for CRP when compared to the control group (p=0.07) but this was not evident for TNF-α

(P=0.541). One study (41) of arginine, omega-3 fatty acid and nucleotide enhanced EN only reported baseline CRP so the effect of intervention could not be evaluated. The same study showed comparable but significant ($p<0.05$) increases in TNF-α for both groups between start and end of treatment (41) with no significant difference between groups (although the p-value was not reported). One study of omega-3 fatty acids reported no overall difference in CRP (43), while another, despite measuring baseline and end of treatment CRP, did not report significance between groups (45). A final study of omega-3 fatty acids reported a decrease in TNF-α in both groups between start and end of treatment; although there was a greater decrease in the immunonutrition group this did not reach significance (p=0.154) (42).

Effect on dual pro and anti-inflammatory cytokines

IL-6 was reported in three studies (42)(44)(46) (Table 2c). One study of omega-3 fatty acids showed a significant decrease in IL-6 between start and end of treatment (p=0.031) when compared to the control group (42). A similar decrease in IL-6 was seen in another study of arginine, omega-3 fatty acid and nucleotide supplementation but this did not reach significance (p=0.083) over the intervention period (46)). Conversely, one study of omega-3 fatty acids in NSCLC patients showed an increasing trend of IL-6 in both groups during the intervention period (444) .

Effect on anti-inflammatory cytokines

IL-10 was reported in two studies, one of oesophageal cancer (46) and one of oesophageal and head and neck cancer (46) (Table 2d). A study of arginine, glutamine and fish oil showed maintenance of IL-10 in the immunonutrition group with a significant decrease in IL-10 in the control group ($p<0.05$) (41). In the same study the ratio of IL-12/IL-10 (pro/anti-inflammatory) was maintained in the immunonutrition group but tended to be higher in the control group (p=0.1) (41). The other study of arginine, omega-3 fatty acid and nucleotide supplementation observed a decrease in IL-10 between the start and end of treatment in the immunonutrition group but it didn't reach significance (p=0.069) (46).

Secondary outcomes

Nutritional status and intake

Sanchez-Lara et al. was the only study that reported changes in intake of energy and macronutrients (44). They showed supplementation with the omega-3 fatty acid EPA maintained dietary intake and lead

to an increased total caloric intake compared to the reduced dietary intake seen in the control group (44). One study reported energy intake only (35); the other studies didn't report baseline energy or protein intake.

Four studies reported baseline nutritional status using a validated tool (41)(42)(43)(44). One study used Kondrup Score (NRS-2002) and Subjective Global Assessment (SGA) (42), two used SGA only (43)(44), and one used Nutritional Risk Index (NRI) (41). Fietkau et al. (42) also used an SGA score of B or C and a Kondrup score (NRS-2002) of $\geq$3 as part of the inclusion criteria and this was the only study to report changes in nutritional status. There was a significant improvement in both Kondrup score (NRS-2002) ($p=0.0165$) and SGA ($p=0.0065$), with 28.6% vs 3.3% of patients treated with omega-3 fatty acids having an improved SGA score and no patients showing worsening SGA. No studies described stratification by nutritional risk during recruitment; however, there were no significant between group differences in nutritional risk where baseline measures were taken (41)(42)(43)(44).

Other measures of nutritional status taken at baseline included weight (40)(41)(42)(43)(44)(46), BMI (41)(42)(44)(45), percentage weight change (41)(44) and measures of body composition (42)(44)(45). There were no significant differences between groups in these baseline measures.

A significant between group difference ($p=0.01$) in weight was reported in one study, with weight loss in the control and weight maintenance in the immunonutrition group (45).

Change in BMI was reported in two studies of omega-3 fatty acids (42)(45); both immunonutrition and control groups showed a decrease in BMI between start and end of treatment, with no statistically significant difference between groups. Difference in percentage weight change was reported in one study of EPA, arginine and nucleotides (44). Although there was no significant between group difference, there was significant weight loss in the control group over the course of treatment (2.8% $\pm$ 5; $p=0.002$) but not in the immunonutrition group (0.54% $\pm$ 4; $p=0.733$) (44).

Changes in body composition were reported in three studies (42)(44)(45). Techniques of assessment included psoas major muscle area using CT (45) and bioelectrical impedance analysis (42)(44)(45). Akita et al. showed a dose-dependent response to changes in body composition; psoas major muscle area ratio ($p<0.001$) and SMM ratio ($p=0.042$) significantly increased in patients who took more than

50% of their allocated EPA-fortified supplement (45). Those that took less than 50% of their allocated EPA dose tended towards greater muscle loss in line with the control group. A similar mean muscle gain was observed in another study of EPA fortification (p=0.01) (44).

No studies reported energy expenditure or activity levels, nor did they report potential sources of incidental nutritional losses (i.e. diarrhoea, vomiting).

Discussion

This systematic review identified seven studies of 521 patients with upper gastrointestinal tract, head and neck, lung, ovarian and pancreatic cancer from multiple countries. The heterogeneity of the existing trials precluded metanalysis and the limited identified evidence in this review means that we are unable to conclude if immune-enhanced enteral formula support (i.e. immunonutrition) brings about an improvement in immune function and infection during chemotherapy.

Chemotherapy associated infections have significant impact on patient health and on health system costs (4). Immunonutrients have been shown to reduce infectious complications, improve markers of immune function and reduce inflammation in surgical cancer patients (37)(48) but understanding of their role during chemotherapy is lacking with some evidence of increased infections (49). The acute metabolic insult and stress event caused by surgery leads to a hypermetabolic state and a period of acute inflammation (50), which may be amenable to modulation using immunonutrition. Evidence of reductions in infectious complications (25)(48)(49), shorter length of stay (25)(26)(30) and better cost effectiveness (25) is most compelling in patients undergoing surgery for upper gastrointestinal cancer. Despite this, translation of this approach into the chemotherapy setting has been less compelling (49). Chemotherapy, rather than one acute stress event, involves multiple cycles of treatment with a complex, cyclic and iterative impact on immune cell function (51) including transient lymphodepleted states. When these are coupled with the more prolonged metabolic effects of chemotherapy (52)(53)(54) and cytokine mediated inflammation from the tumour (55), highly variable changes in nutritive demand on the patient occur. Radiation has also been shown to elicit an immune response and stimulation of the inflammatory cascade (56). Despite this, we were surprised to find no studies of immunonutrition that reported absolute numbers of infectious episodes as a primary or secondary outcome in this patent group. Where events were reported, they were grouped under haematological or non-haematological AEs.

When considering the impact of immunonutrition on innate or adaptive immune response there was significant between study variation in the inflammatory cytokine response to immunonutrition and variability in outcome reporting. Only one study of Neomune (containing omega-3 fatty acids, glutamine and arginine) delivered via gastrostomy in patients with oesophageal cancer showed a significant decrease in inflammatory markers, TNF-α and CRP, alongside a trend to reduction in IL-6 and maintenance of the anti-inflammatory cytokine IL-10 (46). A similar study utilising the same product in a mixed population of patients (head and neck, cervical and oesophageal cancers) did not report inflammatory markers (40), so the reproducibility of this formulation in other cancer groups could not be confirmed. Mechanistically each component of this formulation has been shown to have a potential modulatory role on inflammation and to support cell-mediated immune responses. Omega-3 fatty acids have anti-inflammatory properties (11)(57): they downregulate production of eicosanoids from arachidonic acid mitigating against their pro-inflammatory and immunosuppressive effects (10). They also reduce production of classic pro-inflammatory cytokines including TNF-α (11). Arginine increases the number of T helper cells in the bloodstream (58), while glutamine enhances glutathione production and promotes T and B cell responses to immune stimulation (59). In periods of catabolic stress during cancer, glutamine can become conditionally essential (16) and thus patients may benefit from glutamine provision. However, glutamine is metabolised at a high rate by both cancer and immune cells and there is a lack of information on the tumour response to increased glutamine availability (60). As well as the potential importance of the exact composition of any immunonutrition formula and its mode of action, systemic inflammatory status may be affected by type of cancer and extent of disease. Within the included studies, CRP levels were usually similar between groups in a single study, but between studies CRP varied quite markedly, possibly indicating differences in inflammatory states in some cancers or with some treatments. A study of omega-3 fatty acid supplementation in lung cancer showed a significant reduction in CRP and TNF-α in the intervention group (45). However, a study of head and neck/oesophageal cancer patients showed a significant increase in TNF-α (42). Changes in immune cell numbers with immunonutrition were unclear. One study showed increased numbers (leukocytes, neutrophils, monocytes and lymphocytes) with immunonutrition (41) but another did not (CD3, CD4 and CD8 cells, leukocytes, polymorphonuclear cells and lymphocytes) (46), so no clear conclusion can be drawn. Talvas et al. (41), despite the small sample size (N=28) of their study, showed some alterations

in immune cell phenotype and receptor gene expression which may suggest underlying mechanisms for some of the immunological benefits of immunonutrition; these effects require further investigation.

Heterogeneity of study designs meant we were unable to elucidate an optimal composition, dose, timing or duration of immunonutrition. Immunonutrition delivered via tube feeding (PEG or NG) did however, result in better compliance and a tendency towards an anti-inflammatory state compared with delivery via ONS. For secondary outcomes there was also evidence of a dose-dependent response in one trial. This study showed significant improvements in skeletal muscle mass only in patients who had more than 50% of their daily dose of 2.0 g EPA and 0.85 g DHA (42). A daily dose of 2.2 g EPA is recommended as part of clinical guidelines in cancer cachexia (6)(32). Poor compliance was attributed in part to a dislike of product taste, particularly for omega-3 fatty acid fortified supplements. However, studies of pharmacologically delivered (via tablets or IV infusion) omega-3 fatty acids during chemotherapy have shown good compliance (61)(62) alongside reductions in infectious complications (63), but these studies were not considered as part of this review. Enteral nutrition delivery has several potential benefits: nutrient delivery to the lamina propria, part of the gut-associated lymphoid system, is important to support immunological surveillance via nutrient-sensing pathways such as the aryl hydrocarbon and retinoic acid systems (64). Nutrient delivery to the gut supports microbial diversity either directly or via effects on the immune system (65) and can maintain barrier integrity and function (66), reducing risk of bacterial translocation.

Timing of delivery of immunonutrition may also be key. Subgroup analysis of surgical studies found the most significant improvements in infectious outcomes occurred when immunonutrition was either delivered preoperatively (5 to 7 days) (67)(25)(68) or to malnourished patients (68)(69)(70). In the current review pre-loading of 3 (44) or 5 days (42) was used in two studies but neither saw significant changes in outcome, despite >70% compliance. In the context of chemotherapy, the value of immunonutrition during periods of lymphodepletion, particularly in the case of haematological patients, is not understood and cell recovery or duration of neutropenia were not reported consistently in the studies included in this review. In these studies, reported outcome collection was prior to cycles of chemotherapy alongside concurrent radiotherapy (40)(41)(44)(46) or pre and post radiotherapy (42)(45). Where patients received weekly chemotherapy and the outcomes were collected during

radiotherapy (40)(46), there is the potential for greater inflammation, but this would be the same for both the immunonutrition and control groups.

Aside from immunonutritions potential role in supporting immunological function in order to mitigate the risks of infection, there is extensive and increasing interest in the role of immunonutrition in management of malnutrition and cachexia. Malnutrition is present in 20-70% of cancer patients (6)(7) impacting on treatment completion rates (71)(72), infection (72) and length of stay (73). Malnourished patients have environmental enteric dysfunction showing alteration of gut structure and function (74) and impaired cell-mediated immunity (75). Hence, nutrition support is a widely-used therapy in such patients (76)(55). Systemic inflammation in cachexia leads to an upregulation of inflammatory cytokines, muscle apoptosis, appetite suppression and metabolic changes (27)(55) with a heightened inflammatory state associated with adverse outcomes during chemotherapy (77). Treatment with omega-3 fatty acid enriched ONS has shown benefits in cachexia (76). One of the studies of omega-3 fatty acid enhanced immunonutrition suggested an association between decreased CRP and maintenance of dietary intake (45) in the immunonutrition group. Within this review no study stratified recruitment by degree of malnutrition, cachexia or inflammation; however, there were no significant differences between groups in baseline BMI and CRP in any study. Interestingly many of the studies also provided either more energy (40)(44) or protein (9 to 31g/d) (40)(42)(43)(45) in the group receiving immunonutrition than in the control group. As dietary intake, malnutrition or cachexia were not routinely measured over the course of the studies, we are unable to interpret the impact of this difference on reported outcomes.

This systematic review was rigorous in nature in order to capture all appropriate studies, with a two-step process for quality assessment. We supported inclusion of both clinical presentations of infection and blood biomarkers of immune function and inflammation (CRP, cytokines, immune cell numbers) to explore the potential effect of immunonutrition on both innate and adaptive immunological pathways. Despite this, there are some limitations of the review. Not all relevant papers could be included: four were excluded due to being published in a language other than English (2 in Chinese (78)(79) and 2 in Japanese (80)(81)) and one paper was unavailable (72). Of those excluded due to language, the abstract (in English) of the study by Cong et al (78) reported a significant reduction in infection-associated complications in the immunonutrition group (6% vs 19%, $p<0.05$). The paper that was

unavailable (82) explored the impact of 2 g/d EPA on inflammatory profiles of oral cavity cancer patients but reported no significant difference in CRP or IL-6 between groups. Heterogeneity in immunonutrient composition, volume and delivery, population and outcomes precluded a metanalysis. The range of possible immune outcomes was limited to circulating CRP and cytokine concentrations and blood numbers of different immune cell types. There are normal ranges for CRP and for numbers of different immune cell types. Although CRP, cytokines and immune cell numbers are considered clinically meaningful markers of inflammation and immune status, a deeper evaluation of immunity through assessments of immune function such as natural killer cell or cytotoxic T cell activity would be highly valuable and should be considered in future studies. A full discussion of markers of immunity and inflammation may be found elsewhere along with a consideration of the meaning of changes in such markers (83)(84)(85), although this discussion was not in an oncology context.

The overall risk of bias was classified as “some concerns for all studies”; this was mainly due to a lack of detail in reporting or limited protocol access to evaluate methods of randomisation, blinding and statistical analysis plans. Some studies reported issues with recruitment and compliance which could have affected the significance of the reported outcomes. Cost effectiveness of immunonutrition was not evaluated in any study.

Conclusion

Adult cancer patients should have access to pathways that support the diagnosis, assessment and treatment of nutritional deficiencies during chemotherapy as part of routine care (6). To our surprise very few studies have been conducted to assess the role of immunonutrition on infective outcomes in this group of patients despite the proposed role of improving immune functioning. As such, the role of immunonutrition as a nutritional intervention for adult cancer patients to support improvements in immune function during chemotherapy is uncertain and requires further research. It is imperative that high quality RCTs include well characterised patient populations (to account for potential disease specific metabolic variations), and characterise, identify and treat baseline and recurring nutritional deficits using well defined enteral immunonutrient formulae. The impact of provision of immunonutrition during lymphodepleted periods of treatment on leukocyte recovery is warranted. It is essential that studies involving chemotherapy clearly report the timing of immunonutrient delivery in relation to

radiotherapy, chemotherapy (number of days) and immune cell depletion and cell recovery (days of lymphodepletion/neutropenia). We suggest studies explore provision at the following time points: pre-chemotherapy, during lymphodepletion and post lymphodepletion to assess the impact of immunonutrition on immunological markers and infectious episodes. Studies of immunonutrition in overnourished cancer patients or those with diabetes with higher infection risks during chemotherapy would help inform clinical practice. Designs should aim to ensure isocaloric isonitrogenous controls and account for the degree of malnutrition either as a confounder or in randomisation with intervention and control concealment wherever possible.

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The authors declare no conflicts of interest

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