Anti-cytokines in the treatment of cancer cachexia

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Cancer-related cachexia (CRC) is a multidimensional, frequent and devastating syndrome. It is mainly characterized by a loss of skeletal muscle tissue, accompanied or not by a loss of adipose tissue that leads to impaired functionality, poor quality of life, less tolerability to cancer-directed therapies, high levels of psychosocial distress, and shorter survival. Despite its clinical importance, there is a lack of effective pharmacological therapies to manage CRC. Pro-cachectic cytokines have been shown to play a critical role in its pathogenesis, providing the conceptual basis for testing anti-cytokine drugs to treat this paraneoplastic syndrome. The aim of this review was to examine the current evidence on anti-cytokines in the treatment of CRC. Several anti-cytokine agents targeting one or more molecules (i.e., TNF-alpha, IL-1 alpha, IL-6, and others) have been investigated in clinical trials for the treatment of CRC, mainly in phase I and II studies. Results have been mixed, and few drugs have demonstrated positive effects in larger phase III trials. Thalidomide, a derivative of glutamic acid with anti-inflammatory, immunomodulatory, and anti-angiogenic properties, and MABp1, a natural IgG1k human monoclonal antibody against IL-1 alpha, have shown the most prominent clinical benefits. Studies have recruited heterogeneous cancer patient populations in late disease stages, and many had issues with accrual and attrition. Anti-cytokines remain a promising treatment strategy in the treatment of CRC. Agents targeting multiple CRC cytokines and pathways, while also possessing anti-tumor effects, such as thalidomide and MABp1, have attained the most interesting outcomes, and warrant further investigation. Future studies including more homogenous populations, using valid and clinically meaningful outcome measures and testing low toxicity drugs in earlier stages of the cancer cachexia continuum might achieve better results.

Keywords: Cancer; cachexia; cytokines; treatments

Introduction

Cancer-related cachexia (CRC) was recently defined by an international panel of experts as a "multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (1). It is recognized as a distinct entity from age-related loss of muscle mass, starvation, primary depression, malabsorption, and hyperthyroidism (2). Although the frequency of CRC may vary depending on the definition and criteria used for its diagnosis, it is considerably high (60–80%) (3-6), particularly among patients with lung, head and neck, upper gastrointestinal malignancies, and some aggressive forms of lymphomas (7,8). Important clinical findings of cachectic cancer patients include different degrees of weight loss, anorexia, fatigue, decreased muscle strength,

68

Prado and Qian. Anti-cytokines for cancer cachexia

reduced fat-free mass index, and biochemical disturbances such as anemia, low serum albumin, and high inflammatory markers (2). As compared to non-cachectic patients, patients suffering from CRC have lower levels of functionality, worse quality of life, more frequent treatment-related toxicity, and shorter overall survival (9-11). Furthermore, CRC is a source of psychological distress for both patients, and their caregivers (12-14).

Unfortunately, despite the clinical importance of this frequent and devastating syndrome, there are no broadly adopted guidelines to standardize its management (15). Moreover, there is a lack of effective pharmacological interventions to treat CRC, and current management mostly relies on non-pharmacological approaches such as nutrition education, and support, as well as exercise (16). Pharmacological agents that have been recommended as reasonable options in managing cancer cachexia are symptom-directed drugs like corticosteroids, and progesterone analogs (17-19). Although beneficial, the positive effects of these drugs are mainly on the anorectic component of the CRC syndrome, and their clinical use is limited by their side effect profile (19,20). Agents that have also been studied for the management of CRC include natural compounds (i.e., eicosapentanoic acid) (21,22), ghrelin analogs (i.e., anamorelin) (23,24), COX-2 inhibitors (i.e., celecoxib) (25,26), selective androgen receptor modulators (i.e., enobosarm) (27,28), synthetic cannabinoids (i.e., dronabinol) (29,30), anti-cytokines (i.e., thalidomide) (31,32), and others (33). In this article, we reviewed the current evidence on anti-cytokine interventions for the treatment of CRC as these constitute promising strategies to effectively manage this syndrome.

Pathogenesis of CRC and the role of cytokines

Although recent research has progressed in eliciting the underlying biological mechanisms driving the development of CRC, a complete understanding of its etiology and pathogenesis is yet to be achieved (34). Nevertheless, the hypercatabolic state triggering skeletal muscle and adipose tissue depletion in CRC is thought to be the consequence of a variable combination of different mechanisms, including alterations in energy balance with high levels of resting energy expenditure (REE) and reduced energy intake; hormonal and metabolic disturbances, both peripherally and in the central nervous system (CNS); and a pro-inflammatory/pro-cachectic environment induced by tumor byproducts and immune-system mediators (35). Among the

several tumor and immune-system-derived inflammatory and pro-cachectic factors involved in the pathogenesis of CRC, cytokines such as IL-6, IL-1 beta, TNF-alpha, TWEAK (TNF-related weak inducer of apoptosis), and others, seem to play a central role in the development of CRC as they can determine proteolysis and lipolysis by a direct effect on target tissues, or indirectly by disrupting CNS controls of appetite and metabolic processes (35,36). Their central role on CRC pathogenesis has been suggested by studies conducted both in animal and in human subjects. In preclinical studies, for example, IL-1, TNF-alpha, and IL-6 have been linked to the development of weight loss, skeletal muscle catabolism, and adipose tissue depletion in rodents (37-39). On the other hand, blocking the same mediators with the administration of anti-cytokine antibodies was able to attenuate cachexia in animal tumor models (40,41). Also, gene knockout mice for the TNF-alpha receptor type I protein had less muscle wasting as compared to their wild-type counterparts in a fast-growing mouse tumor-induced cachexia model, highlighting the importance of TNF-alpha in the skeletal muscle depletion of CRC (42). Similarly, in clinical studies involving human subjects with different cancer types, high levels of peripheral inflammatory cytokines (i.e., IL-6, TNF-alpha) have been also associated with clinical and biochemical markers of cachexia like weight loss, low body mass index, high REE, and decreased levels of serum albumin, total protein, and hemoglobin (43-45). Taken together, these studies have supported the important role of inflammatory cytokines and pro-cachectic mediators in the pathogenesis of CRC, and, thus, have provided the rationale for the development of anti-cytokine agents to manage this common paraneoplastic syndrome. *Figure 1* describes the core biological mechanisms of CRC pathogenesis, and the main targeted anti-cytokine treatments discussed in this review.

Anti-cytokine agents for CRC

Thalidomide

Thalidomide is a derivative of glutamic acid that has been shown to possess anti-inflammatory, immunomodulatory, anti-angiogenic, sedative and anti-emetic effects (46,47). Although its mechanism of action is not completely understood, it seems to involve the suppression of several cytokines (i.e., TNF-alpha, IL-6), and angiogenesis mediators (i.e., VEGF, FGF), as well as the inhibition of NF-kappa B and downregulation of COX-2 (48). Because
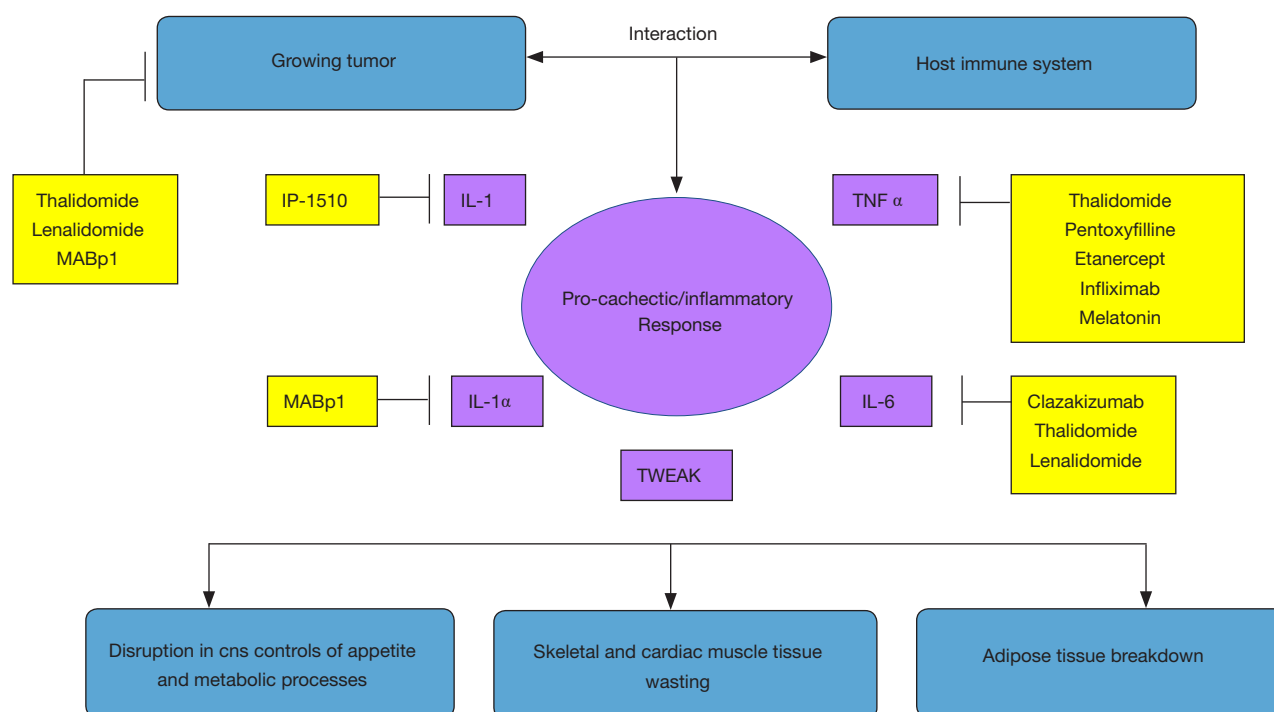
Figure 1 Core biological mechanisms involved in CRC pathogenesis and main anti-cytokine targeted treatments under investigation. CRC, cancer-related cachexia; IL, interleukin; TNF, tumor necrosis factor; TWEAK, TNF-related weak inducer of apoptosis; CNS, central nervous system.

of these properties, thalidomide has been studied in the management of auto-immune conditions like Bechet's disease, and rheumatoid arthritis (49), as an anti-neoplastic therapy in different tumor types (49,50), and in the treatment of cachexia, and its related symptoms caused by malignant and non-malignant diseases such as the HIV-associated wasting syndrome (51,52). In the treatment of CRC, several clinical trials have studied the use of thalidomide in doses ranging from 100 to 200 mg/day, as a single agent or in combination with other interventions to manage cachexia in different cancer populations (31,53-60). At least five of the CRC trials evaluating thalidomide were randomized controlled (*Table 1*) (31,55,56,58-60). In the first of these, Gordon *et al.* compared thalidomide 200 mg daily for 24 weeks with placebo in a population of inoperable pancreatic cancer patients with more than 10% of weight loss in the last 6 months, and a life expectancy ≥6 weeks (31). Fifty patients were randomized to both arms, and 33 were evaluable (pre-planned evaluable sample size was 34 for the primary endpoint analysis at week 4). While patients in the placebo group lost an average of 2.21 kg of body weight (primary endpoint), and 4.6 cm³ of bone free muscle mass

as measured by dual-energy X-ray absorptiometry (DEXA), patients receiving thalidomide gained 0.37 kg [absolute difference $=-2.59$ kg, (95% CI, -4.3 to -0.8), P=0.005], and 1.0 cm³ [absolute difference $=-5.6$ cm³ (95% CI, -8.9 to -2.2, P=0.002] in weight, and arm muscle mass, respectively. Thalidomide was overall well tolerated (31). In a similar study design, Wilkes *et al.* have also tested thalidomide (200 mg/day) against placebo, but using a slightly different drug exposure period (6 weeks), and in a different population of incurable esophageal cancer patients with life expectancy of more than 8 weeks (56). No specific CRC diagnostic criteria were employed for patient inclusion. Thirty-four patients were randomized to the two study groups. However, because of a high attrition rate due to disease progression, elective withdrawal, and drug toxicity, only 8 patients were evaluable in the thalidomide group at week 6, compromising the study power to detect outcomes differences between arms. No statistically significant differences between study groups were found in any of the primary [eight change, and lean body mass (LBM) by DEXA] or secondary endpoints (REE by indirect calorimetry, other body composition measures,

Table 1 Randomized-controlled trials of anti-cytokines in the treatment of cancer-related cachexia

Reference	Agent/phase	Population	Size	CRC criteria	Study arms	Outcome measures[†]	Main results
Gordon et al. 2005	Thalidomide; phase II	Inoperable pancreatic cancer	50 pts; 33 evaluable	Weight loss >10% in last 6 months	(a) Thalidomide 200 mg/day; (b) placebo; duration: 24 weeks	(I) Weight change at week 4; (II) bone free muscle mass, grip strength, QoL, and survival	Improved weight, and bone free arm muscle mass
Mantovani et al. 2010	Thalidomide; phase III	Different advanced cancer types	332 pts; all evaluable	>5% loss of ideal or pre-illness weight in last 3 months, with or without abnormal inflammatory cytokines	(a) Medroxyprogesterone acetate 500 mg/day or megestrol acetate 320 mg/day; (b) EPA supplement (2.2 g/day); (c) L-carnitine 4 g/day; (d) Thalidomide 200 mg/day; (e) combination of a, b, c, and d; duration: 4 months	(I) LBM, REE, and fatigue; (II) appetite; grip strength; QoL; serum IL–6, and TNF-alpha; ROS, and GPX blood levels; prognosis by GPS; AEE and TEE; ECOG-PS	LBM, REE, and fatigue improved in combination arm as compared to arms (c), and (d)
Wilkes et al. 2011	Thalidomide; phase II	Incurable esophageal cancer	34 pts; 24 evaluable	No specific CRC criteria	(a) Thalidomide 200 mg/day; (b) placebo; duration: 6 weeks	(I) Change in weight, and LBM; (II) REE; triceps skin-fold thickness, and mid-arm circumference; Karnosfky Index, fatigue, levels of TNF-alpha, and IL-1-beta, symptoms of disease progression, safety, and survival	No significant differences between groups for all outcomes
Yennurajalingam 2012	Thalidomide; phase II	Different advanced cancer types	31 pts; 21 evaluable	>5% weight loss within last 6 months, reporting anorexia, fatigue, and one more symptom (≥3/10 anxiety, depression, or sleep disorders) in last 24 h	(a) Thalidomide 100 mg/day; (b) placebo; duration: 2 weeks	(I) Anorexia-cachexia symptom cluster; (II) body composition, REE, and serum cytokines	No between-groups statistically significant differences were found
Wen et al. 2012	Thalidomide; phase II	Different advanced cancer types	108 pts; 93 evaluable	≥5% loss of ideal or pre-illness weight in last 3 months	(a) Megestrol 320 mg/day and thalidomide 100 mg/day; (b) Megestrol 320 mg/day; duration: 8 weeks	(I) Weight, fatigue, and QoL; (II) appetite, grip strength, prognosis by GPS, ECOG-PS, IL-6, and TNF-alpha	Improved weight, fatigue, QoL, grip strength, GPS, and ECOG as well as decreased IL-6, and TNF-alpha in combination arm

Table 1 (*continued*)

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Reference	Agent/phase	Population	Size	CRC criteria	Study arms	Outcome measures †	Main results
Goldberg et al. 1995	Pentoxifylline; phase II	Different advanced cancer types	70 pts; all evaluable	Weight loss ≥5 lb within last 2 months, or an estimated caloric intake <20 kcal/kg/day	(a) Pentoxifylline 400 mg t.i.d; (b) placebo; duration: until loss of clinical benefit	(I) Weight change; (II) appetite, perceived food intake	Stopped at interim analysis due to futility; no between-group differences were found
Mehrzad et al. 2016	Pentoxifylline; phase II	Different advanced cancer types	70 pts; 64 evaluable	>5% loss of ideal or pre-illness weight in last 2 months	(a) Pentoxifylline 400 mg t.i.d; (b) placebo; duration: 8 weeks	Changes in weight, arm circumference, and QoL ‡	No between-group significant differences were found, except an improvement in QoL in pentoxifylline group at week 4
Jatoi et al. 2007	Etanercept; phase II	Different advanced cancer types	66 pts; 63 evaluable	Weight loss of ≥2.27 kg within last 2 months and/or an estimated caloric intake <20 kcal/Kg/day	(a) Etanercept 25 mg twice weekly; (b) placebo; duration: 24 weeks	(I) Non-fluid weight gain; (II) anorexia, QoL, TNF-alpha polymorphisms, safety, survival	Terminated early due to low accrual; no between-group statistically significant differences were found
Wiedenmann et al. 2008	Infliximab; phase II	Advanced pancreatic cancer	89 pts; 51 evaluable	≥10% premorbid weight loss or ≥5% within last 90 days	(a) Infliximab 3 or 5 mg/kg at weeks 0, 2, 4 and then every 4 weeks; (b) placebo; all: Gemcitabine 1 g/kg weekly ×6; then 3 weeks on, 1 off; duration: 24 weeks	(I) Change in LBM; (II) OS, PFS, KPS, 6-minute walk test, fatigue, anorexia, pain, QoL, and safety	No between-group significant differences were found
Jatoi et al. 2010	Infliximab; phase II	Elderly, and/or poor performance status metastatic NSCLC	64 pts; 61 evaluable	No specific CRC criteria	(a) Infliximab 5 mg/kg/day on day 1, weeks 1, 3, and 5 (first 8-week cycle), then day 1 on weeks 1 and 5 every 8 weeks; (b) placebo; all: Docetaxel 36 mg/m² 6 weeks on, 2 weeks off; duration: 4–6 months	(I) >10% non-fluid weight gain; (II) anorexia, QoL, fatigue, TNF-alpha polymorphisms, tumor response, PFS, safety, and survival	Terminated early due to low accrual; no between-group statistically significant differences were found
Del Fabbro et al. 2013	Melatonin; phase II	Advanced lung or GI cancer	73 pts; 48 evaluable	Appetite score ≥4 on a 0–10 scale (10= worst) and ≥5% weight loss within last 6 months	(a) Melatonin 20 mg at night; (b) placebo; duration: 28 days	(I) Appetite improvement; (II) weight, LBM, cancer-related symptoms, and QoL	Closed at the interim analysis for futility; no between-group statistically significant differences were found

Table 1 (*continued*)

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Reference	Agent/phase	Population	Size	CRC criteria	Study arms	Outcome measures †	Main results
Rigas et al. 2010	Clazakizumab (ALD518); phase II	Advanced NSCLC	124 pts §	>5% weight loss within last 3 months; CRP >10 mg/dL	(a) ALD518 80, 160, or 320 mg every 8 weeks; (b) placebo; duration: 24 weeks	(I) Safety; (II) LBM, lung cancer symptoms, fatigue, anemia	ALD518 group had less loss of LBM at week 12, and improved lung symptom, and fatigue scores at week 2
Hichish et al. 2017	MABp1; phase III	Metastatic colorectal cancer	333; 309 evaluable	Any weight loss ≤20% in last 6 months or serum IL-6 ≥10 pg/mL plus anorexia, fatigue or pain (EORTC QLQ-C30 >10), and decreased role, emotional, and social function (score <90)	(a) MABp1 7.5 mg/kg every 2 weeks; (b) placebo; duration: 8 weeks	(I) Stable or increased LBM and stability or improvement in 2 of 3 symptoms (fatigue, pain, and anorexia; (2) inflammatory response, functional performance, QoL, tumor response, safety, and survival	More patients in MABp1 group achieved the composite primary outcome; MABp1 group had lower IL-6, less thrombocytosis, and longer survival

†, (I) primary outcome; (II) secondary outcomes. ‡, primary and secondary outcomes not specified. §, data on evaluability not available. AEE, active energy expenditure; CRC, cancer-related cachexia; CRP, C-reaction protein; ECOG-PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C-30, European Organization for Research and Treatment of Cancer QLQ-C30; EPA, Eicosapentaenoic acid; GI, gastrointestinal; GPS, Glasgow prognostic score; GPX, antioxidant enzyme glutathione peroxidase; KPS, Karnofsky performance status; LBM, lean body mass; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; Pts, patients; QoL, quality of life; REE, resting energy expenditure; ROS, reactive oxygen species; TEE, total energy expenditure; T.I.D, three times a day.

Karnofsky Index, fatigue by Piper questionnaire, serum levels of cytokines, and survival). Nine of the 17 patients on thalidomide arm had drug-related adverse events, mainly rash, and hypersomnolence (56). More recently, in another placebo-controlled randomized trial designed to evaluate the effects of thalidomide (100 mg/day) on anorexia-cachexia-related symptoms, body composition, resting metabolic rate, and serum cytokines in a population of advanced cancer patients with various tumor types, Yennurajalingam *et al.* have also had issues with poor accrual and high attrition rates that probably influenced the study outcomes (58). From the 31 patients that entered the study, a third dropped out before the study's primary endpoint analysis at day 15, mainly because of hospitalization due to disease progression, and non-adherence. The authors found no between-group difference in the outcomes evaluated. Toxicity was minimal and none of the patients withdrew because of thalidomide-related adverse events (61). In contrary to the limited results attained by small randomized trials that investigated single-agent thalidomide, many of which were also underpowered due to high attrition rates, studies evaluating thalidomide in combination with other interventions, and in larger cohorts had more encouraging results (55,59). In a 5-arm single-center trial, Mantovani *et al.* randomized 332 advanced cancer patients with a ≥5% loss of ideal or pre-illness weight within last 3 months, and life expectancy of ≥4 months, to receive one of the following interventions: (I) medroxyprogesterone 500 mg/day or megestrol acetate 320 mg/day; (II) 2.2 g/day of oral supplementation with eicosapentaenoic acid; (III) L-carnitine 4 g/day; (IV) thalidomide 200 mg/day; and (V) a combination of all interventions. Final analysis at week 16 comparing only arms 3, 4, and 5 (arms 1, and 2 were withdrawn because they fulfilled inferiority rules in the pre-planned interim analysis), showed that the combined intervention was significantly superior to other arms for the primary outcomes of LBM by DEXA (P=0.007), REE by indirect calorimetry (P=0.028), and fatigue (P=0.035) as measured by the Multidimensional Fatigue Symptom Inventory-Short Form. All patients in this study were evaluable (55). Finally, in a more recent trial using the same CRC, and prognostic criteria as the prior 5-arm study, Wen *et al.* randomized 108 advanced cancer patients to megestrol acetate (320 mg/day) alone or in combination with thalidomide (100 mg/day) for 8 weeks. The combination arm had significant improvements in primary endpoints of body weight (P=0.025), fatigue (P<0.01), and quality of life (P=0.01) as compared to single agent megestrol.

In addition, combination therapy group had also better ECOG-PS (P=0.02), and grip strength (P=0.05), as well as lower Glasgow Prognostic Score (P=0.02), and lower levels of TNF-alpha (P=0.01), and IL-6 (P<0.01) (59). The mixed results achieved by these randomized clinical trials have prevented thalidomide to be recommended as a pharmacological therapy in the management of CRC in clinical practice. Nevertheless, because of its broad mechanisms of action targeting multiple pathways involved in CRC pathogenesis, overall good tolerability when used in doses below 200 mg/day, and its low cost, at least in developing countries (62), it still remains an attractive agent that warrants further research as a CRC treatment option. Lenalidomide, a derivative of thalidomide with similar properties of the parent compound, is also being investigated for the treatment of CRC in a randomized-controlled clinical trial. Results of this study are not yet available (63).

Pentoxifylline, etanercept, infliximab, and melatonin

TNF-alpha has been suggested to be one of the key pro-inflammatory mediators involved in the pathogenesis of CRC (33,36). This has been supported by both preclinical and clinical data, and has provided the conceptual basis for the development of anti-TNF strategies to treat the CRC syndrome (38,41,42,44). Pentoxifylline, a blood viscosity reducer agent; the monoclonal antibodies etanercept, and infliximab; and melatonin, a pleotropic hormone used to treat sleep disturbances, have been investigated in clinical trials as anti-TNF therapies for managing the CRC syndrome (32,64-67). The methylxanthine derivative pentoxifylline was the first drug within this group to be tested in CRC randomized-controlled trials. Unfortunately, these studies failed to demonstrate any beneficial effect of pentoxifylline to advanced cancer patients with cachexia. In a multicenter study conducted by the North Central Cancer Treatment Group, pentoxifylline (400 mg, three times a day) was not better than the identical placebo in improving body weight, appetite, or perceived food intake in a population of 70 advanced cancer patients with ≥5% loss of ideal or pre-illness weight in the previous 2 months from study entry. The trial was closed earlier due to futility (32). Negative results with pentoxifylline for managing CRC have also been observed in a recent randomized placebo-controlled trial conducted in a cohort of cachectic advanced cancer patients in Iran. After 8 weeks of follow-up, no statistically significant difference were

74

Prado and Qian. Anti-cytokines for cancer cachexia

found between pentoxifylline and placebo groups in study outcomes except for a better quality of life as measured by the Short Form 36 survey (SF36) in the anti-TNF arm at week 4 that was not anymore found in the 8-week analysis (64). Similarly to what have been observed in the pentoxifylline clinical trials, both the monoclonal antibodies etanercept, and infliximab have shown no benefit in treating cancer cachexia (65-67). In a proof-of-concept multicenter clinical trial, Jatoi *et al.* randomized 64 advanced cancer patients expected to live 3 or more months to receive the dimeric fusion protein etanercept (25 mg/day subcutaneous twice weekly) during 24 weeks or placebo during the same period. The trial was terminated earlier due to low accrual, and no significant differences were observed between etanercept and placebo in non-fluid weight gain, patient-reported symptoms, quality of life or survival (65). The same group of researchers also tested the anti-TNF monoclonal antibody infliximab to treat cachexia in a population of 64 elderly, and/or poor performance status non-small cell lung cancer (NSCLC) patients. The cohort was randomized to receive infliximab (5 mg/kg/day on day 1, weeks 1, 3, and 5 in the first 8-week cycle, then on day 1, weeks 1 and 5 every 8-week cycle) for 4–6 months or placebo. All patients received docetaxel (36 mg/m^2 intravenously, 6 weeks on, 2 weeks off) during the same period. This trial was also stopped earlier due to low accrual. As compared to placebo, patients in the intervention group had more fatigue, and worse functional and physical well-being. No benefits were found with infliximab therapy (66). Another randomized controlled trial comparing infliximab plus gemcitabine versus gemcitabine plus placebo in cachectic patients with stage II–IV pancreatic cancer have also had negative results (67). Finally, melatonin has been evaluated in the treatment of CRC. Although non-blinded and/or non-placebo controlled studies were able to demonstrate positive effects of the use of melatonin as anti-CRC agent, this was not confirmed in a recent randomized, double-blind, placebo-controlled trial that investigated the use of melatonin (20 mg at night) for managing anorexia and other CRC-related symptoms in a population of advanced lung or gastrointestinal cancer patients. The study was closed at the interim analysis for futility (68). Despite that none of these anti-TNF agents were beneficial in CRC clinical trials, it is not possible to reject the prior evidence pointing to the central role of TNF-alpha in CRC pathogeneses, as issues such as low accrual, sample size, and the use of drugs that interfere with only one of the multiple cytokines involved in the development of CRC may have prevented these studies to have positive results.

MABp1

IL-1 alpha has been shown to be an early mediator of the inflammatory response, triggering the synthesis of other cytokines, and driving both tumor growth and cachexia (35,37,69-71). Thus, it has also been identified as an attractive therapeutic target in the management of the CRC syndrome. MABp1, a natural IgG1k human monoclonal antibody targeting IL-1 alpha has been recently evaluated as a new pharmacological treatment of CRC and its related symptoms (72,73). Interesting findings were first demonstrated in an open-label, phase I, dose-escalation trial to evaluate MABp1 safety, and tolerability. In this study, 52 metastatic cancer patients were exposed, every 3 weeks, to four dose levels of intravenous MABp1 (0.25, 0.75, 1.25, and 3.75 mg/kg). Therapy was overall well tolerated with proteinuria, nausea, and fatigue being the most frequent possibly drug-related side effects. In addition, as compared to baseline, patients completing the 8-week secondary outcomes assessments had significant improvements in mean LBM as assessed by DEXA (P=0.02), fatigue (P=0.008), appetite loss (P=0.02), and pain (P=0.02) symptom scores, as well as social (P=0.04), emotional (P=0.03), role function (P=0.006), and quality of life (P=0.02) scores as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C30). From 34 patients evaluable for tumor response, 10 had stable disease and one had a partial response (72). More recently, a larger, multicenter, double-blind, placebo-controlled phase III trial evaluated the effects of MABp1 on a composite primary endpoint that included patient-reported (EORTC-QLQ-C30), and body composition assessments (LBM by DEXA). Three hundred and thirty three advanced colorectal cancer patients with any involuntary weight loss ≤20% within last 6 months or ≥10 pg/mL serum IL-6 and who also had disease-related symptoms (>10 points in EORTC-QLQ-C30 anorexia, fatigue or pain symptom scores), and impaired quality of life (<90 points in EORTC-QLQ-C30 role, emotional, and social function scores) were randomly allocated to receive MABp1 (7.5 mg/kg IV) every 2 weeks for 8 weeks or placebo. As compared to placebo, a higher proportion of patients in the Mabp1 group achieved the combined primary endpoint (33% *vs.* 19%, P=0.004) at week 8. Also, exploratory secondary outcomes analysis showed that patients in the intervention arm had significantly lower levels of serum IL-6 (1.6 *vs.* 9.9 pg/mL,

P=0.01), and thrombocytosis (14×10^9 vs. 40×10^9/L, P=0.005) as well as longer median survival (6.1 vs. 2.4 months, P=0.0002). There were no significant differences in the rate of adverse events between groups. The most common grade 3 adverse events in MABp1 group were anemia (4%), fatigue (3%), peripheral edema (2%), and abdominal pain (2%) (73). Despite these promising results, more research is needed to establish a role for this agent in the management of CRC.

Clazakizumab

The observation that IL-6 inhibition is able to detain the development of cachectic features in preclinical animal studies has raised the interest in targeting this pro-inflammatory/pro-cachectic factor also in the clinical setting (40,74). Although several anti-IL-6 drugs are currently under development, the humanized monoclonal antibody clazakizumab, previously ALD518 or BMS-945429, is the only specific anti-IL6 agent that has been evaluated in clinical trials for the treatment of CRC (75-78). After a phase I study demonstrating the safety of clazakizumab in a small cohort of 9 advanced cancer patients, a phase II study was conducted in a population of 124 incurable NSCLC patients diagnosed with cachexia defined by >5% loss of body weight within last 3 months (76-78). Patients were randomly assigned to receive one of three doses of intravenous clazakizumab (80, 160, or 320 mg) every 8 weeks for 24 weeks or placebo. Only 29 patients were able to complete all the pre-planned study evaluations during the 6-month period. The majority either died due progressive disease (n=52) or failed to attend all the scheduled study visits (n=38). A preliminary pooled analysis including patients receiving any of the three clazakizumab doses revealed that, as compared to placebo, the intervention group had a lower proportion of patients losing more than 5% of LBM as measured by DEXA (3% vs. 20%, P=0.05) at week 12, and reported better lung symptoms score (15.1 vs. 14.1, P<0.0006) and fatigue score (22.9 vs. 21.3, P=0.025) at week 2 as assessed by the Functional Assessment of Cancer Therapy—Lung Cancer Subscale, and the Functional Assessment of Chronic Illness Therapy-Fatigue, respectively. One patient had a serious adverse event (rectal hemorrhage) considered possibly related to clazakizumab. No significant differences between clazakizumab and placebo study groups were observed in the rate of serious adverse events. The most common adverse effects in the intervention group were

dyspnea (18%), chest pain (11%), and hemoptysis (11%) (76,78). Further research on this and other anti-IL-6 CRC agents are warranted.

Other anti-cytokine agents

Other two anti-cytokine drugs, IP-1510, a synthetic IL-1 receptor antagonist, and OHR/AVR118, a peptide-nucleic acid that has immunomodulatory, and anti-inflammatory properties by acting on different cytokines, have been investigated for the treatment of CRC (79,80). Preliminary results of a small phase I/II clinical trial to evaluate safety and toxicity of the administration of IP-1510 (1 mg subcutaneous twice a day for 28 days) given to a population of advanced cancer patients were presented at the 6th Cachexia Conference in Milan, Italy. No specific CRC diagnostic criteria were reported for patient inclusion. The majority (evaluable =20/29) were able to complete the scheduled treatment, and the drug was deemed to be well tolerated with no serious adverse events being described. Additionally, 17 patients gain or stabilized their weight, and significant improvements were noticed in the Karnofsky performance status (P≤0.01), and in the Edmonton Symptom Assessment Scale (ESAS) appetite (P≤0.01), and depression scores (P≤0.01) (81,82).

With regards to the use of the peptide-nucleic acid OHR/AVR118 to manage CRC and its related symptoms, the most recent clinical data was also presented in an international cachexia conference (83). In this phase I/II study conducted in a population of stage III–IV cancer patients, Chasen *et al.* investigated the effects of OHR/AVR 118 (4 mL subcutaneous once a day) for 28 days on appetite, early satiety and nutritional intake as measured by the ESAS, Dyspepsia Symptom Severity Index, and the patient-generated subjective global assessment. As compared to baseline, evaluable patients completing study assessments (n=18) had significant improvements in appetite (P=0.001), and nutritional status scores (P=0.025). At the end of the treatment period, body weight, fat, and muscle mass was also stabilized. The authors reported that drug tolerability was good (83). Final results of studies evaluating these two agents are still pending publication.

Conclusions and future perspectives

Although preclinical and clinical research studies have made progress in understanding the pathogenesis of CRC, and in identifying biological pathways that could possibly

be targeted with pharmacological therapies, there are still no effective drugs approved for the treatment of CRC and its related symptoms, and it remains an unmet clinical problem. The use of agents targeting cytokines involved in the pathogenesis of CRC has emerged as an attractive strategy to manage the syndrome. However, the majority of clinical trials evaluating anti-cytokines CRC therapies were not able to achieve positive outcomes. This can be explained by several reasons. Until recently, there were no consensus-based CRC definition, diagnostic criteria, or classification system developed specifically to reflect the particular characteristics of cachexia of the adult cancer population, which have resulted in the inclusion of very heterogeneous patient populations in CRC clinical trials. Also, most studies recruited patients at or approaching the late disease stages, with short life expectancy, when cachexia might be already refractory to clinical interventions, and when the possibility of attrition due to disease progression or death is very high. Moreover, many anti-cytokines tested have no anti-cancer effect and have a very limited mechanism of action, in which only one or few pro-cachectic mediators are targeted. Interestingly, thalidomide (either alone or in combined interventions) and MABp1, drugs that have shown to interfere with multiple CRC cytokines and pathways, while also possessing anti-cancer properties, were the anti-cytokines agents that have demonstrated the most prominent clinical benefits in larger phase II or III clinical trials, confirming the need of using a multitarget pharmacological therapy to address CRC complex underlying mechanisms. Therefore, based on the evidence built until now, anti-cytokines agents continue to be a promising CRC therapy. To achieve better outcomes and overcome methodological challenges, the design of future CRC clinical trials involving anti-cytokines will need to include standardized inclusion criteria, valid, and clinically meaningful outcome measures, and the use of low toxicity therapies targeting multiple and redundant pro-cachectic molecules and pathways in earlier phases of the cancer cachexia continuum. This might make possible that an anti-cytokine is added to a multimodal approach to manage CRC multidimensional syndrome.

Acknowledgements

Footnote

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78

Prado and Qian. Anti-cytokines for cancer cachexia

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