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Abstract

The American Society of Clinical Oncology (ASCO) 2024 Annual Meeting highlighted several developments in supportive care, emphasizing innovative approaches to enhance care through novel interventions and personalized symptom management. This narrative review synthesizes and critically evaluates four of the main studies in supportive care presented: "REACH PC Trial: Comparative effectiveness trial of early palliative care delivered via telehealth versus *in person among patients with advanced lung cancer" by Greer J,* et al*; "MENAC Trial: Results from a randomized, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with advanced cancer undergoing chemotherapy" by Solheim T,* et al*; "MC2 Trial: A randomized, double-blind controlled trial of medicinal cannabis* vs *placebo for symptom management in patients with advanced cancer receiving palliative care" by Hardy J,* et al*; and "Alliance A222001 Trial: A randomized, double-blind, placebo controlled phase II study of oxybutynin versus placebo for the treatment of hot flashes in men receiving androgen deprivation therapy" by Stish B,* et al*. The aim is to provide a comprehensive overview of studies that address symptom management and quality of life (QoL), while emphasizing the clinical implications of the results presented.*

Introduction

At ASCO 2024, several pivotal studies were presented, advancing the understanding and application of supportive care in oncology. These studies explore innovative approaches to symptom management, the integration of multimodal interventions, and the potential of emerging therapies to alleviate the burden of cancer.

One key study presented in a plenary session at the congress, the REACH PC trial, was a comparative effectiveness trial evaluating the delivery of early palliative care via telehealth versus in-person consultations for patients with advanced lung cancer (Abstract 1).[1] This study addressed the growing need for accessible and flexible palliative care options, highlighting the increasing use of telehealth platforms in clinical practice.

Another important study, the MENAC trial, investigated a multimodal intervention combining exercise, nutrition counselling and supplementation, and anti-inflammatory medications compared to standard care alone, in attenuating cachexia among patients with advanced cancer undergoing palliative systemic treatment (Abstract 2).[2] Cachexia remains a major challenge in oncology, and this study offers insights into potential strategies for its management.

The role of medicinal cannabis in symptom management was explored in the MC2 trial, a randomized, double-blind controlled trial comparing cannabis to placebo in patients with advanced cancer receiving palliative care (Abstract 3).[3] As interest in the therapeutic use of cannabis continues to grow this study provides further evidence to help clarify its role in the field.

Lastly, a phase 2 study, the Alliance A222001 trial, focused on the treatment of hot flashes in men undergoing androgen deprivation therapy (ADT) for prostate cancer (Abstract 4).[4] This randomized, double-blind, placebo-controlled trial evaluated the effectiveness of oxybutynin, in mitigating this common and distressing side effect of ADT.

This narrative review will explore the main findings of these studies, focusing on their implications for clinical practice.

Abstract 1 – REACH PC Trial: comparative effectiveness trial of early palliative care delivered via telehealth versus in-person among patients with advanced lung cancer [1]

Early palliative care is established as a cornerstone of comprehensive advanced cancer care. In advanced lung cancer, the early delivery of palliative care has been shown to improve QoL, symptom management, and possibly extend survival.[5] As healthcare technology advances, delivering palliative care via telehealth has become an area of interest.

The REACH PC trial was a randomized trial evaluating early palliative care through monthly telehealth *vs* traditional in-person visits among patients with advanced lung cancer.[1] The main inclusion criteria were: adult patients diagnosed with advanced non-small cell lung cancer, with and ECOG PS of 0 to 3, receiving cancer care with a non-curative intent. The primary aim was to compare the effectiveness of both systems based on the QoL assessed by FACT-L. Secondary aims included satisfaction with care, caregiver attendance at visits, and mood symptoms. Statistical analysis estimated differences in week-24 scores. This study was conducted in a single country, the United States of America, across 18 states.

A total of 1250 patients were randomized between the two arms, with balanced patient characteristics between groups including treatment type. Of note, at the 24-week mark, 66% patients in the telehealth arm had completed the FACT-L questionnaire versus 69% in the in-person visits arm. The study demonstrated the equivalence of the effect of delivering early palliative care via video *vs* in-person on patients' QoL with FACT-L adjusted means of 99.67 *versus* 97.67, $p<0.043$ for equivalence. Regarding the secondary outcomes, the rate of caregiver participation in the visits was lower in the telehealth *versus* in-person group (36.6% *versus* 49.7%, $p<0.0001$), while satisfaction with care and mood symptoms did not differ between groups.

The authors concluded that equivalence of the effect of delivering early palliative care through video *versus* in-person visits was demonstrated. Indeed, this meticulously designed study represents high-quality evidence that telehealth-delivered palliative care seems to be effective, and it could lead to a paradigm shift in how it is delivered, making it more accessible and convenient for patients while also potentially reducing costs. However, there are still limitations in the conclusions that can be made from this study. Generalization of results to other cancer populations is not possible, since the study populations is certainly not representative of the different geographic areas of the world, or socioeconomic groups. In fact, these outcomes are very likely limited by factors such as patient access to technology, digital literacy, and regional variations in healthcare delivery. Patients' willingness to have telehealth consultations may also represent a limitation in the practical applicability of these results, in fact, in this study about 47% of the approached patients declined participation, which reflected in the long accrual of about 5 years.

Telehealth has increasingly been integrated into cancer care and is a clear area of interest in cancer clinical research, with the COVID-19 pandemic providing a unique impetus for its adoption and expansion. However, evidence is still limited, and there is a particular lack of studies directly comparing telehealth to in-person interventions,[6] similar to the REACH PC trial.[1] The existing evidence collectively highlights the promise of telehealth in enhancing cancer care and potentially making it accessible to more patients, while also pointing to the need for strategies to address potential barriers to its widespread implementation.

In summary, in clinical practice, the shift of palliative care to telehealth offers many potential benefits while also raising important questions about the quality, accessibility, and sustainability of care, since it could compromise the depth of patient-provider interactions, exacerbate disparities particularly for patients who lack access to reliable internet, technology, or are uncomfortable with digital platforms, and pose challenges in symptom management and long-term care sustainability.

Abstract 2 – MENAC Trial: Results from a randomized, open-label trial of a multimodal intervention (exercise, nutrition and anti-inflammatory medication) plus standard care versus standard care alone to attenuate cachexia in patients with advanced cancer undergoing chemotherapy [2]

Cachexia, characterized by severe muscle wasting and weight loss and commonly observed in advanced cancer patients, is multifactorial and driven by systemic inflammation and metabolic disruptions within the tumor microenvironment.[7] It seems to significantly worsen cancer treatment out-

comes by potentially increasing toxicity, treatment delays, and dose reductions. It is also seems to be associated with poorer overall prognosis. Treatment of cancer-related cachexia remains limited, with interventions more often focusing on symptom management rather than addressing the underlying metabolic and inflammatory pathways.

The MENAC trial was a randomized, open-label clinical, multicenter study designed to assess the impact of a multimodal intervention on cancer cachexia.[2] The trial included patients with stage III or IV pancreatic or lung cancer undergoing systemic anticancer treatment who were randomly assigned to two groups: one receiving standard care alone, and the other receiving a multimodal intervention that included a combination of exercise, nutritional support, omega-3 supplements, and ibuprofen. The primary outcome was difference in weight change, while secondary outcomes included difference in muscle mass and physical activity.

A total of 212 patients were included with generally balanced patient characteristics between groups. The study met its primary outcome, with a lower mean weight change in the multimodal arm versus the standard of care group (0.05 *vs* -0.99 kg, mean difference -1.04kg, 95%-CI -2.02 to -0.06, *p*=0.04). There were, however, no differences between arms regarding muscle mass loss and mean step counts.

The authors concluded that that weight loss was prevented by the multimodal treatment, and that their results provided background for further research on cachexia.

While this study does provide new insights in a field where high-quality is lacking, it does have a few limitations. Firstly, while preventing or minimizing weight loss in cancer patients is an important goal, its significance lies in whether it translates to improved treatment tolerance, the ability to maintain optimal dosing, and how it impacts QoL. Unfortunately, this trial did not provide, and may not have assessed, data directly related to these outcomes. Secondly, it is important to question what was the individual impact of all elements of the multimodal approach – are they all needed? Lastly, the trial did not succeed in demonstrating an effective strategy for preserving muscle mass, which remains a significant unmet need in the management of cancer cachexia.

In summary, treatment options for cancer-related cachexia remain highly limited, with current strategies focusing on managing symptoms rather than reversing the underlying metabolic and inflammatory processes. While nutritional support and exercise interventions can help prevent weight loss, they frequently fail in maintaining muscle mass. Other options under investigation, such as ponsegromab, a monoclonal antibody that targets metabolic pathways associated with cachexia, offer hope by potentially preventing muscle wasting and addressing this critical gap.[8]

Abstract 3 – MC2 Trial: A randomized, double-blind controlled trial of medicinal cannabis vs placebo for symptom management in patients with advanced cancer receiving palliative care[3]

Medicinal cannabis and derived products are becoming increasingly used by patients with advanced cancer, despite that, evidence of their benefit as a supportive care measure is still lacking.[9]

The MC2 trial is an investigator-initiated trial that aimed to assess the impact of tetrahydrocannabinol (THC) added to cannabidiol (CBD) *versus* placebo in symptom control of patients with advanced cancer. This study was preceded by the MC trial, in which CBD alone did not improve symptom management beyond that provided by standard palliative care alone. Key inclusion criteria were: patients with advanced cancer and baseline Total Symptom Distress Score (TSDS) ≥10/90 based on Edmond Symptom Assessment Scale. The main outcome measure was change in TSDS from baseline at day 14.

A total of 145 were randomized. The trial was negative for its primary outcome, while symptom scores improved in both arms from baseline to day 14, there were differences in response (≥6 score decrease in TSDS in THC plus CBV *vs* placebo: 44.6% *vs* 49.2%, *p*=0.75%). Pain was the only isolated symptom to with a significant decrease in ESAS score, while all other individual symptoms had no difference in score between arms.

The authors concluded that a significant benefit is achieved y the delivery of palliative care alone, since both arms saw a decrease in symptom burden. Additionally, that THC plus CBD led to a small benefit in pain at the expense of increased toxicity, namely neuropsychiatric symptoms.

While approaching a key clinical question regarding the use of medicinal cannabis, the study was negative for its primary outcome. The presented data lacks a detailed description of patient characteristics, such as cancer type and stage, comorbidities, types of anticancer treatments delivered, which are crucial for understanding the trial's generalizability, suggesting a likely heterogeneous population which may have potentially impacted the results.

In summary, medicinal cannabis has yet found a clear place in the treatment of advanced cancer. Recent ASCO guidelines clearly state patients should be recommended against the use cannabis or cannabinoids as a cancer-related treatment, while also mentioning that current evidence only points to a potential improvement in refractory, chemotherapy-induced nausea and vomiting when added to guideline-concordant antiemetic regimens.[9] Furthermore, there is evidence suggesting the possible immunosuppressive effects of cannabis, which could negatively impact immune checkpoint inhibitors effects and outcomes.[10]

Abstract 4 – Alliance A222001 Trial: A randomized, double-blind, placebo controlled phase II study of oxybutynin versus placebo for the treatment of hot flashes in men receiving androgen deprivation therapy [4]

Hot flashes are a common side effect experienced by men with prostate cancer being treated with ADT, with reported frequencies during treatment up to 80%.[11] While pharmacological treatment with gabapentin and megestrol acetate has shown to contribute to symptom control, additional symptom control is needed.

The Alliance A222001 trial was a randomized, double-blind, phase 2 trial that aimed to assess the benefit of oxybutynin for the treatment of hot flashed in men under treatment with ADT. Patients were randomized between oxybutynin 5 mg, oxybutynin 2.5 mg, and placebo. Included patients had to be men receiving ADT with at least 28 hot flashed per week; concurrent use of abiraterone was allowed, however other novel androgen receptor inhibitors were prohibited due to being metabolized by CYP and their potential interaction with oxybutynin. The primary objective was to evaluate efficacy of both dosages of oxybutynin compared to placebo, assessed by a hot flash score.

A total of 88 patients were accrued, with balanced baseline characteristics between arms. Patients reported an average of 10.15 hot flashes per day and an average daily hot flash score of 18.23 at baseline. The high dose oxybutynin arm had a greater reduction in daily hot flash scores *versus* placebo (13.95 *vs* 4.85, $p = 0.002$), as did low dose oxybutynin arm patients (9.94 *vs* 4.85, $p = 0.07$). Regarding safety, there were no treatment-related grade ≥3 adverse events, and the most frequently reported grade 2 adverse event was dry mouth.

The authors concluded that oxybutynin significantly improved hot flash scores and frequency compared to placebo, and it was well tolerated without important toxicity.

In summary, this study does suggest oxybutynin may be another pharmacological option in the treatment of ADT-related hot flashes, with minimal toxicity. However, an important limitation of the study and its use in clinical practice is the potential for interactions with second-generation androgen receptor inhibitors, aside from abiraterone, which may restrict its use in many patients.

Conclusions

The studies here discussed highlight developments in personalized supportive care strategies, including the integration of digital health into daily care and novel interventions designed to ease the burden of cancer-related symptoms. Emphasis was placed on the clinical implications of these studies. Remarkably, the REACH PC trial was presented during a plenary session of the ASCO 2024 Annual Meeting, highlighting the growing recognition of supportive care as an essential component of comprehensive cancer treatment and research. However, supportive care in cancer still receives less attention and research compared to cancer treatment itself, with trials in this area often meeting significant challenges as shown in the presented trials, such as slow patient accrual and extended trial durations.

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