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Mini Review

Time to Test More Anti-Cancer Treatment Strategies in the Elderly

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Abstract

Cancer is linked to ageing, which is a well-known risk factor. Because of the growing senior population, the number of new cancer diagnoses has increased globally. Many theories have been proposed over the years to explain this increased risk, including higher genetic and epigenetic alterations, as well as the idea of immunosenescence. The best therapeutic options for this cancer-stricken population are unknown. Older cancer patients have historically been underrepresented in clinical trials designed to establish best practises, resulting in undertreatment or higher toxicity. With this in mind, it's critical to look into new anti-cancer agents, such as immune-checkpoint inhibitors, that have recently been discovered, in order to manage these daily clinical issues and eventually combine them with alternative antiblastic drug administration strategies, such as metronomic chemotherapy.

Keywords: Older patients • Cancer • Immunosenesce • Metronomic chemotherapy • Immunotherapy

Introduction

Although older cancer patients make up the majority of clinical oncology practise, there are fewer data on the risks and benefits of cancer treatment in this group, owing to their under-representation in most clinical trials that establish international standards of care [1-3]. This problem is exacerbated in the elderly population (over 80 years old) and, in general, leads to undertreatment of this group due to a lack of understanding of anti-cancer drug tolerability and efficacy [4].

As a result, further research into this subject is required to gain a better understanding of the potential treatment plans for older cancer patients, including engaging them in clinical trials aimed at determining their optimal standard of care and alternative treatment techniques. We looked at the most common cancer therapy options for older cancer patients, with a particular focus on a potential novel therapeutic technique for this group of individuals.

Epidemiologic and Mechanistic Data

Patients over the age of 65 account for approximately 50% of new cancer diagnoses and 70% of cancer-related death in the United States [5]. A similar trend may be seen in Europe, where more than half of newly diagnosed cancers are in those over the age of 65 [6]. Aging is a well-known risk factor for cancer development due to numerous causes [7,8]. The most researched variables include genetic and epigenetic alterations, mitochondrial malfunction, endocrine and cytokine-mediated mechanisms, mutations in aged stem cells, and telomere shortening [9,10]. Immunosenescence is another mechanism underlying the link between ageing and cancer growth. This is marked by a decrease in the number of naive CD8 T+ and CD4 T+ cells in the peripheral blood, which is caused by the involution of immune system components. The ability of T-cells to be activated and fulfil their activities is reduced as a result of these elements, even in tumour growth control, boosting immune escape, which is one of the key hallmarks of cancer cell proliferation.

3. Chemotherapy Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) idea underpins traditional chemotherapy, which is infusing a chemotherapeutic medication at the highest dose that causes manageable side effects. This approach has been used to treat haematological malignancies since the 1960s, demonstrating for the first time an effective treatment strategy for these disorders. However, due to the loss of a significant fraction of highly reproducing normal cells, such as those lining the gastrointestinal system and bone marrow cells, MTD chemotherapy is associated with a not insignificant set of adverse effects.

In general, in the younger population, the cost-effectiveness of toxicity is well balanced, especially with the development of supportive medications such as antinausea or granulocyte-stimulating factors (G-CSF), which reduce the most prevalent side effects associated with chemotherapy regimens.

For a variety of reasons, the same outcomes are not accessible for older cancer patients. The loss in function of end organs is linked to ageing. Slower drug metabolism, for example, may affect liver function, which is linked to greater chemotherapy dose exposure for longer periods if hepatically cleared. The similar thing happens with renally cleared drugs as glomerular filtration decreases over time. The reserve in the bone marrow declines with age, causing patients to have extended cytopenias. Myelosuppression is a "qualitative" issue that ought to be explored, not only a quantitative one of MTD treatment. High-dose chemotherapy, in particular, impairs immunological tolerance by causing natural killer (NK) and γδT cell malfunction. Furthermore, high-dose chemotherapy can harm dendritic cells (DCs), diminishing their antigen-presenting function, decreasing their motility, and suppressing the expression of cell surface markers. Other considerations include the fact that elderly cancer patients are typically fragile, have a variety of comorbidities at the time of diagnosis that may limit chemotherapy tolerability, and use a large number of medicines that may interact with anti-cancer treatment. Finally, in recent decades, more and more data on chemotherapy-induced cognitive deficits has been documented.

All these aspects limit clinicians in treatment decision making, leading to recommendations of best supportive care rather than chemotherapy given the potential risks. Several prediction tools have been developed specifically on this topic, such as: Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score, able to stratify the patients in four risk categories of severe toxicity; chemotherapy toxicity calculator from the Cancer and Aging Research Group (CARG score), a predictive model for chemotherapy toxicity in patients ≥65 years old; and Geriatric 8 score (G8), a screening tool to determine which older cancer patients should undergo full geriatric evaluation prior to commencing chemotherapy.

4. Metronomic Chemotherapy

Low-dose Metronomic Chemotherapy (MC), an alternate method, has been studied in recent years to reduce the drawbacks of MTD chemotherapy and to try to overcome resistance mechanisms. Its purpose is to deliver low-dose chemotherapy without interruption, and it has been evaluated in a number of studies including a variety of histologies.

Through a variety of ways, this new scenario offers numerous options for combating cancer cell proliferation and acquired tumour resistance. The effect of MC on tumour cell development pathways and its impact on the tumour microenvironment are its most intriguing features. Tumour cells, in particular, require the formation of new blood vessels in order to meet their high energy demands as a result of their fast growth, a process known as angiogenesis. Blood vessel genesis is aided by Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factors (FGF), Platelet-Derived Growth Factor (PDGF), Epidermal Growth Factor (EGF), and Thrombospondin-1

(TSP-1). Tumor cells produce a large percentage of them. In this context, MC has been demonstrated to cause apoptosis and endothelial migration in activated endothelial cells, as well as inhibit the function of key angiogenesis factors.

The immune system has another effect on the tumour cell microenvironment. Immune escape is one of the most essential and well-studied characteristics of cancer cell proliferation, as previously stated. It entails the creation and stimulation of immunosuppressive molecules in order to suppress both the innate and adaptive immune responses and prevent tumour invasion and elimination.

Treg cells, which suppress tumor-specific effectors (CD8+ T lymphocytes, CD4+ T helper cells, and NK cells), and myeloid-derived suppressors (MDSCs), which suppress T and NK cells through distinct pathways, are both implicated in this challenge. MC has been shown to augment host immunity through a variety of immunomodulatory mechanisms in recent years. Continuous exposure to a low dose of cyclophosphamide, for example, stimulated the release of pro-inflammatory factors (IL-6 and IL-12) through macrophages, downregulated anti-inflammatory cytokines (TGF-) and IL-10, and reduced Treg numbers in vitro. Methotrexate, paclitaxel, vincristine, and vinblastine at low concentrations increase DC maturation and antigen-presenting function.

The benefits of MC are not only biological, but they are also important in clinical settings. MC, in particular, has a strong anti-cancer activity and survival benefit in the most important oncologic outcomes, such as overall survival and progression-free survival, in a variety of histologies, as well as a favourable safety profile, particularly in older cancer patients. Capecitabine and vinorelbine are the two most investigated drugs in this situation. Even when these medications were given in combination at a metronomic dosage, the advantages were maintained in older cancer patients. Indeed, doctors are increasingly using this method to treat frail older patients who are unable to undergo a regular chemotherapy regimen.

5. Immunotherapy

The immune system's antitumoral role has been known since William Coley observed that injecting inactivated bacteria into sarcoma sites could cause tumour shrinking.

In recent years, several types of immunotherapies have been studied. Immune checkpoints, specifically cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1), also known as immune checkpoint inhibitors (ICIs), have been of special interest in this respect.

CTLA-4 is expressed on the cell surface of CD4+ and CD8+ T lymphocytes, while PD-1 is found on the surface of T cells, B cells, and NK cells in the immune system. All of these can activate inhibitor pathways in these cells, resulting in a shift in the immunosuppressive landscape, such as in Treg cells. Blocking these inhibitory cell surface proteins has shown to be effective in a variety of cancers, including renal cell carcinoma, melanoma, non-small cell lung cancer, and breast cancer, among others.

These findings were also validated in the senior group, indicating that this therapy technique is effective even in the elderly. The benefit of ICIs in terms of survival is consistent across a 65-year-old age cut-off. However, more information is needed to fully comprehend these findings in people beyond the age of 75. Given that these medications have a diverse side effect profile but are typically well tolerated even in individuals with reduced performance status, this method offers a frequently bearable choice.

6. Metronomic Chemotherapy and Immunotherapy: A New Horizon?

In older individuals requiring combination chemo-immunotherapy, a new model of anti-neoplastic treatment could be combination of low-dose metronomic chemotherapy and immunotherapy. There are data suggesting that certain cytotoxic agents could enhance the efficacy of immunotherapy and further data outlining the immunostimulatory potential of metronomic therapy. Several recent preclinical studies have explored this field outlining promising results.

In one trial, 28 metastatic melanoma patients with progressive disease were treated with a metronomic dose of cyclophosphamide (50 mg twice a day for 1 week altering with off treatment) and celecoxib (200 mg daily throughout the study) followed by vaccination with DCs, showing improved survival compared to retrospective data of treatment without chemotherapy and celecoxib. Encouraging results were found even with the new class of ICI drugs. Karachi et al. demonstrated a relationship between peripheral and tumour immune microenvironment transformation and dose modulation of temozolomide in murine models. Moreover, some data show that the anti-PD1 activity dampens glycolysis, providing cytotoxic lymphocytes with an additional competitive advantage.

Conclusion

In conclusion, both MC and immunotherapy appear to boost immune cell activation, with the former increasing tumor-specific activation and the latter maintaining it. MC has the ability to influence the tumour microenvironment, facilitating tumour invasion and cytotoxicity.

The synergistic effect of low-dose metronomic chemotherapy and immunotherapy provides an encouraging possibility, allowing efficacious treatment while minimising quality of life in frailer patients and opening up a prospective option for those who may have only received supportive care.

Result

Because this cohort is under-represented in clinical trials, anti-neoplastic treatment in older patients remains a challenge. The scientific community should emphasise the need of performing clinical trials in geriatric populations to examine therapy efficacy and safety. The care of these individuals should be interdisciplinary; involving disease specialists and geriatricians, in order to properly evaluate them using proven techniques that can better anticipate how well they will tolerate medicines and how effective they will be. Data from the elderly population has demonstrated that toxicity often prevents older patients from receiving the same dose intensity as younger patients, and the vast majority of geriatric patients will receive less effective and occasionally harmful therapies.

As a result, traditional chemotherapy regimens, including monotherapy and combination regimens, are adjusted in terms of their schedules and dose intensities, lowering efficacy.

To address this problem, current research has shown that combining "new" and "old" medicines, such as immunotherapy with ICIs and MC, may be a viable strategy for preventing cancer progression and resistance. Emerging data has been promising, but it is also premature because it is based on limited clinical experience or in vitro models. Such approaches must be verified in larger, placebo-controlled, randomised studies involving the elderly population, as well as proper clinical evaluation using recognised geriatric instruments. The solid preclinical rationale and favourable toxicity profile of this anti-cancer therapeutic combination appear to be the winning step. It's critical to continue researching these approaches in clinical settings.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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