Review Article

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Winning the Fight Against Cancer

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Abstract

Advances in cytotoxic chemotherapy, surgical oncology, genomic medicine, targeted small molecule treatment, cancer immunotherapy and biology-driven precision radiation oncology have resulted in significant improvements in outcomes of cancer treatment, with an increasing number of patients achieving long-term disease control or even being potentially cured. Concurrent advances in palliative care and geriatric oncology have also helped to ensure that patients are managed holistically by considering their physical, social, psychological and emotional needs in a personalised manner.

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Introduction

The fight against cancer has been a protracted one that has claimed countless casualties across the millennia. Despite numerous advances in modern medicine, it remains a formidable enemy that has overtaken other ailments like infectious and heart diseases to become the leading cause of death worldwide, with an estimated 9.6 million deaths in 2018 alone.[1]

Several analogies have been used for this fight against cancer, including that of a traditional battlefield, where the dreaded disease is seen as an invader while doctors and scientists use all the weapons in their arsenal against the onslaught. However, this analogy is flawed as cancer cells arise from normal cells and the battleground is the patient. We prefer the analogy of the fight against criminal gangs (the cancer) that arise in a city (the patient). The 'criminals' may arise because of genetic mutations (e.g. Li-Fraumeni syndrome) or due to exposure to a toxic neighbourhood environment (e.g. smoking and radiation), and start to proliferate with an intent to gain power and steal the resources of the city. There is a lot more finesse needed for this fight because an all-out battle could lay the entire city to waste.

Traditional Cytotoxic Chemotherapy

Traditional cytotoxic chemotherapy is akin to the heavy artillery used in battle. It hijacks the need for cancer cells to divide by sabotaging the mechanisms for DNA replication. However, normal cells that undergo cell division during chemotherapy would also be affected by this approach. Cells with the shortest cell cycles are those from the bone marrow, hair follicles, skin and gastrointestinal tract, which are therefore the most sensitive to the effects of chemotherapy. Hence, patients receiving cytotoxic chemotherapy commonly have hair loss, gastrointestinal symptoms, skin changes and a drop in blood counts.[2] Moreover, while chemotherapy is moderately effective with cancers with a short replication time, it is less effective with tumours with a slow growth rate such as carcinoid tumours.[3] Early attempts to reduce

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the toxicity of chemotherapy with cytoprotective agents have not been overwhelmingly successful.[4] In recent years, advancements in technology led to new methods to improve the efficacy of cytotoxic chemotherapy. For instance, CPX-351 (liposomal cytarabine-daunorubicin) is a new drug that has been designed to improve the efficacy over the traditional 7+3 cytarabine/daunorubicin chemotherapy regimen for patients with acute myeloid leukaemia (AML).[5] In a Phase III clinical trial comparing CPX-351 with the traditional 7+3 regime, a greater proportion of patients achieved remission with CPX-351 than with 7+3 (47.7% versus 33.3%, respectively; 2-sided P=0.016).[6] It has also shown to improve the patients' quality of life[7] and reduce drug exposure to non-target tissues, which contributes to a more manageable safety profile.[5]

Despite the many side effects, cytotoxic chemotherapy is currently still a backbone used in the frontline treatment of many cancers like acute leukaemia, breast cancer, lymphoma, pancreatic cancer and many others. In fact, conventional cytotoxic chemotherapy still features very strongly in the treatment recommendations of the National Comprehensive Cancer Network for most cancers because of the excellent outcomes.

Surgical Oncology

For many solid tumours, surgery remains the mainstay of curative therapy in situations where the tumour can be completely removed with wide and clear pathologic margins. Surgery also provides important pathological material through which one can study specific prognostic factors, markers or determine subtypes through molecular profiling. Furthermore, the principles of cancer surgery are based on concepts rooted in the biological basis of cancer invasion and metastases.

The 2 most important principles in surgical oncology are as follows: first, to remove the tumour in its entirety with an adequate margin that is deemed clear from microscopic examination. For example, for skin cancer, it is well established that the surgical resection of basal cell carcinoma only requires a 5mm gross margin during surgery;[8] this extends to 1cm in squamous cell cancers and early melanomas, and even wider to 2cm in thicker, more aggressive melanomas.[9] Many of the margin recommendations are tumour- and tissue-specific, but are often also guided by the location of these cancers and the ability to obtain these margins without compromising form and function. For example, it is easy to obtain a wide 5cm margin in tumours arising from the colon, but this becomes more challenging in low rectal cancers, where there may be a desire to spare the anal sphincter for continence. The second major principle in cancer surgery (especially epithelial cancers/carcinomas) is the need to address regional nodal stations. The principle of removing nodal stations requires an approach to remove these by block dissection techniques (as opposed to 'cherry picking' individual nodes), and these are planned in a stepwise manner based on nodal stations. The latter concept varies depending on the cancer type, but in breast cancer and melanomas, the concept of sentinel node dictates that tumours metastasise to one or a few nodes first, before then progressing to subsequent echelons, and hence removing and testing the sentinel node gives important information as to whether the tumour has metastatic potential.[10] However, in many cancers such as gastric or head and neck cancers, this 'stepwise metastasis' model is not as clear-cut, and nodal dissection is based on anatomic levels or 'distance' from the primary tumour and carried out in a systematic *en bloc* manner, ensuring comprehensive nodal clearance for the levels cleared.[11]

Recently, another surgical concept gaining popularity is surgical resection for oligometastatic disease where resection can be conducted *en bloc*, removing the tumour with an adequate margin and if necessary, dealing with regional nodal disease. These are commonly performed in limited liver or lung metastases,[12,13] but also for metastasis to non-standard nodal stations[14] (e.g. cervical nodes for breast cancer). There are limited studies supporting this practice, but it is acceptable if it is technically feasible, does not compromise organ functions and there is a relatively long disease-free interval between the original cancer and metastasis.[15] These types of surgery are usually limited to specific cancer types where there is good supporting data (e.g. colorectal cancer with liver or lung metastasis, renal cell cancers with isolated metastasis, breast cancer with supraclavicular nodal metastasis).[12,16-18] The ability to combine these with newer modalities of treatment, such as targeted and immunotherapy or even proton beam therapy, makes this the most important aspect of surgical oncology research in the near future.

Genomic Medicine and Targeted Small Molecule Treatment

Cancer geneticists are the 'spies' who provide cancer intelligence to help unravel the workings and weaknesses of the enemy by discovering genes found to be mutated in specific malignancies. These mutations can be either somatic or inherited, and can lead to the development of a specific cancer or contribute to resistance to therapy. Approaches developed to target

these mutations have revolutionised cancer care by maximising efficacy while reducing the side effects of treatment. This has been accomplished through increased genetic and genomic testing, which focuses on somatic and inherited mutations, respectively. Technological advancements have given rise to next-generation sequencing (NGS), which allows for a more cost-effective and rapid sequencing of DNA and RNA. Using NGS, studies have found the presence of specific driver alterations found in various different types of tumours,[19] which may lead to the development of cancer therapies targeting multiple tumour types. NGS has numerous platforms with various characteristics—such as differences in sequencing speed or cost—and healthcare institutions can select one or more platforms that most suit their needs. A strategy of upfront identification of hotspot mutations with selection of targeted cases for comprehensive genomic profiling is reasonable.[20] However, for NGS to become a more widely used tool, it will be important to address its lack of accessibility,[21] as well as the cost concerns of the drugs used to target the potential mutations found through the use of NGS. Another significant limitation facing NGS of tumours is that it cannot distinguish between tumour-specific somatic mutations and the patient's germline mutations.[22] To properly identify specific somatic driver alterations, additional genetic testing that identifies germline mutations needs to be conducted to deduct these germline mutations from the somatic mutations. However, germline testing might be difficult to implement owing to strict guidelines on their use, which may result in difficulty in identifying specific somatic driver mutations. To combat this problem, it is imperative for more medical professionals to be trained in performing both genomic and genetic tests, and to encourage them to obtain qualifications to perform these procedures.

Targeted small molecule treatment

Knowledge of the molecular workings of cells and cancer eventually led to the development of targeted therapies, which target specific intracellular pathways or mutant proteins that drive the progression of cancer. Further developments in sequencing techniques have led to a greater understanding of the genes associated with cancer development. In particular, targeting mutations with inhibitors of the mutant gene products has allowed for great advancements in targeted therapies.[23] This has prompted scientists and clinicians to identify cancer-causing genes, and led to the development of biomarkers, as well as specific drugs, to target these mutant genes.

Tyrosine kinase inhibitors (TKIs) are small molecule drugs that target specific tyrosine kinase enzymes, which are upregulated in some cancers. Imatinib is a TKI used to treat chronic myeloid leukaemia (CML), cancers that are caused by the mutated *bcr-abl* protein and cancers caused by c-KIT mutations (e.g. gastrointestinal stromal tumour, acute myeloid leukaemia). It has proven to be much less toxic while being highly efficacious compared to cytotoxic chemotherapy alone[24] or combination therapy of interferon alpha with low-dose cytarabine.[25] These findings have emplaced TKIs as standard of care for patients with CML.[26] Gefitinib is a TKI that has been used to treat cancers caused by a mutated *EGFR* gene, and has shown in clinical trials to be highly effective against cancers driven by such mutations.[27] In a Phase II trial conducted using Gefitinib as a treatment for non-small cell lung cancer (NSCLC) with *EGFR* mutations, it was found that its response rate was relatively higher with less toxicity as compared to conventional cytotoxic chemotherapy.[28] While its ease of administration, promising results and favourable toxicity have led to a rise in the use of TKIs,[29] the problem of eventual acquired resistance limits the efficacy of TKIs, which is exacerbated by the relatively fast rates at which patients develop resistance.[30] While there have been effective second- and third-generation TKIs developed to target this problem, the eventual resistance to these next-generation TKIs limits its efficacy.

The discovery that defects in the ubiquitin-proteasome pathway are associated with certain types of cancer[31] led to the development of proteasome inhibitors as a potential cancer treatment. Bortezomib is a first-generation proteasome inhibitor used in the treatment of multiple myeloma, and is commonly used in conjunction with other agents to improve clinical outcomes in myeloma as well as other lymphoid malignancies.[32,33] Carfilzomib is a second-generation proteasome inhibitor that is also used to treat multiple type myeloma. In clinical trials comparing the use of Carfilzomib plus dexamethasone with Bortezomib and dexamethasone, the use of Carfilzomib plus dexamethasone was found to be superior (Progression Free Survival (PFS) of 18.7 versus 9.4 months).[34]

Cancer Immunotherapy

Cancer immunotherapy aims to amplify the body's immune response against cancer with different methods, such as the use of monoclonal antibodies, adoptive T cell therapy, as well as non-specific immunotherapies (Fig. 1). Other strategies like therapeutic cancer vaccines, cytokine therapy, natural killer (NK) cell

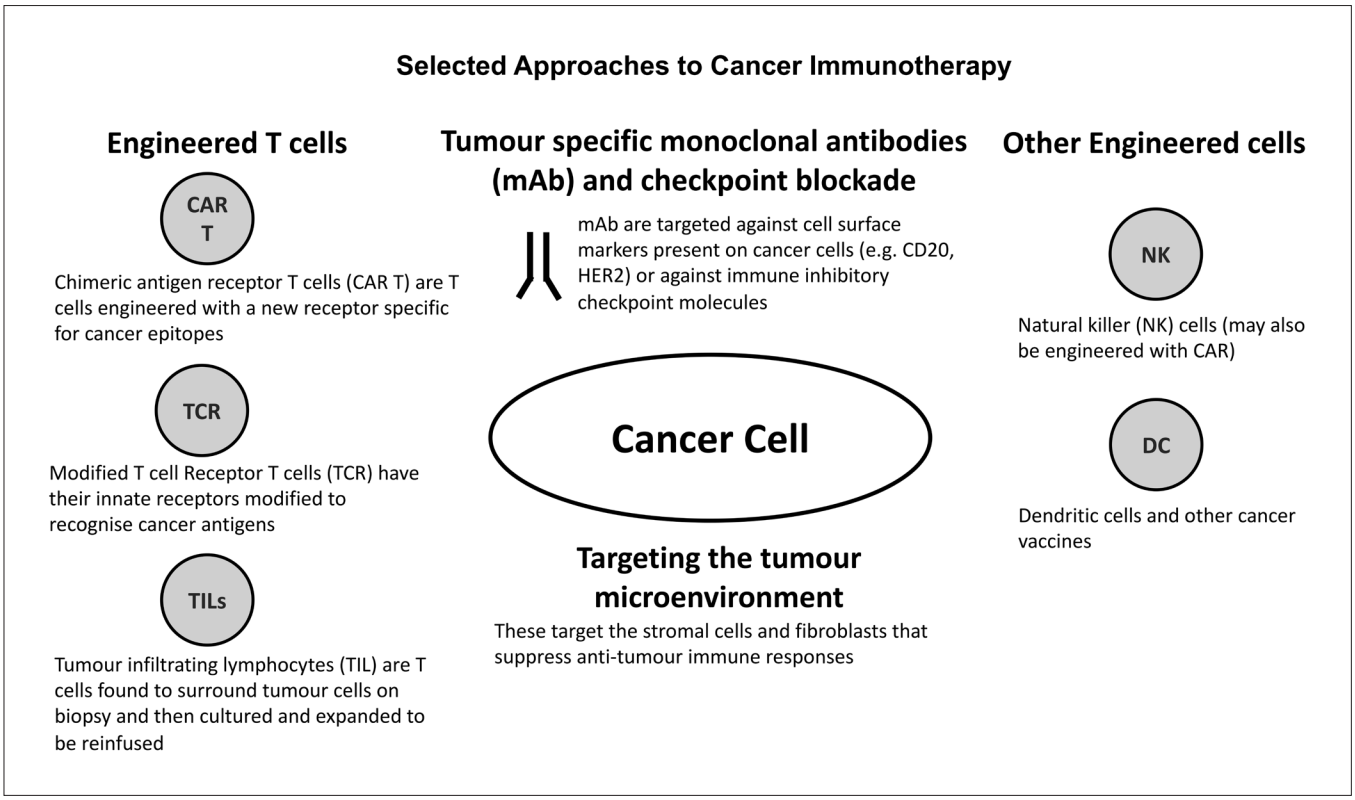

Fig. 1. Selected approaches to cancer immunotherapy include tumour-specific monoclonal antibodies (including checkpoint blockade) and targeting the tumour microenvironment, as well as engineered T cells (which include CAR T cells, modified TCRs and TILs) and other engineered cells (NK and dendritic cells).

therapy and oncolytic virus therapy have modest response rates at present, and need more optimisation.[35]

Monoclonal antibodies, including immune checkpoint therapy

Monoclonal antibodies are like targeted missiles that seek out specific receptors on the cancer cells to destroy them. Rituximab is an engineered monoclonal antibody against CD20 on B cells that has proved tremendously effective in patients with B cell lymphomas, and is now a backbone in lymphoma therapy. Trastuzumab is an antibody against the HER2 receptor on some breast cancers, and around US$7 billion is spent worldwide annually on this drug. Over 47 types of monoclonal antibodies are now in use in oncology,[36] with new ones being added to the inventory each year. While therapeutic monoclonal antibodies like Rituximab and Trastuzumab have improved the prognosis of many patients undergoing cancer treatment, they are expensive and therefore inaccessible to some patients (e.g. average wholesale price of Rituximab per 500mg = US$5,211.78).[37] Multiple biosimilars of these monoclonal antibodies have been developed, such as Rituxirel, which is an approved Rituximab biosimilar that costs up to 84% less than Rituximab.[38] With monoclonal antibodies playing a large part in the fight against cancer, it is likely that the development of their biosimilars will have a big role in reducing costs and improving global access to monoclonal antibody therapy.

Monoclonal antibodies are also used in immune checkpoint therapy, whereby a specific antibody is used to target immune checkpoints, which tumour cells utilise to evade the immune system's antitumour response. Immune checkpoint inhibitors (ICIs) work by amplifying antitumour immune responses by interrupting co-inhibitory signalling pathways and promoting the immune-mediated elimination of cancer cells. Clinical trials on ICIs showed an improvement in survival in cancer patients, which has contributed to rapid Food and Drug Administration regulatory approvals for various types of cancers, such as malignant melanoma, Hodgkin's lymphoma and bladder cancer.[39] Currently, CTLA-4, PD-1 and PD-L1 are the most commonly targeted immune checkpoints.

Ipilimumab is an ICI that binds to CTLA 4, which is a protein receptor present in T cells. Recent clinical trials have proven the effectiveness of Ipilimumab in increasing overall survival in patients with advanced

melanoma,[40] and it has been used in conjunction with other therapies to treat advanced melanoma.[41] Following the approval of Ipilimumab in 2011, other ICIs have been approved for use in various types of cancers, such as Nivolumab, a PD-1 inhibitor, and Atezolizumab, a PD-L1 inhibitor.[42] Immune-checkpoint therapy has provided an increasing number of patients with achieving long-term disease control, as compared to conventional cytotoxic chemotherapy alone.[43] Despite the effectiveness of immune-checkpoint therapy, a large proportion of patients develop side effects (72% with ipilimumab monotherapy and 66% with anti-PD-1/anti-PD-L1 monotherapy).[44] As such, it is imperative to research on methods to manage the toxicities they cause to improve the patient's quality of life during treatment and also to prevent toxicity-related deaths.

Adoptive T cell therapy (ACT)

T cells are the 'policemen' of the body's immune system. They circulate throughout the body looking for potential foreign cells, as well as cells that have changed and become errant (like cancer cells). When they detect abnormal cells, they attack the defective cell while also sending an alert signal to other cells (B cells, natural killer cells and other T cells) to counter the enemy. T cells engineered to target cancer cells include chimeric antigen receptor (CAR) T cells, modified T cell receptor (TCR) cells and tumour infiltrating lymphocytes (TILs).

CAR T cells are T cells that are genetically engineered to express a novel receptor on the cell surface specific for antigens present on the tumour cell surface. This allows the engineered T cells to recognise tumour cells and target them. Clinical trials have shown CAR T cell therapy to be relatively effective against B cell malignancies, such as acute lymphoblastic leukaemia, B cell lymphomas and multiple myeloma.[45,46] Though they are useful in treating some solid tumours, the percentage of patients with complete response to CAR T cell therapy is much higher in patients with haematologic cancers (24.4% to 54.4%) as compared to solid tumours (4.1%).[47] TCR cells, with their ability to recognise intracellular antigens, could be more effective for solid tumours. Currently, the use of CAR T cell therapy is still limited by the need for highly specialised centres and the high cost of treatment (ranging from US$373,000 to $475,000),[48] with an exceedingly high base-case incremental cost-effectiveness ratio.[49]

Tumour-infiltrating leucocytes (TILs) are T cells that have infiltrated the stroma of the tumour, suggesting some form of immune recognition for the cancer cells. TIL therapy makes use of this characteristic by extracting these cells from the tumour, replicating them ex vivo, and then transferring these cells back into the patient alongside a high dose of interleukin-2 (IL-2). Reports have shown that this treatment has been effective against multiple types of cancers, including melanomas,[50] cervical cancers[51] and ovarian cancer.[52] A phase III trial showed a 3-year survival rate of 32–55%,[53,54] as well as complete response in 10–25% of highly advanced melanoma patients who were unresponsive to previous treatments.[55] There is much promise in the potential for TILs to treat patients who may see little improvement from traditional cytotoxic chemotherapy. However, more research should be done to establish the effectiveness of TIL therapy on other types of cancers, and methods to make TIL therapy more accessible to a larger group of patients.

Stromal Cells and the Tumour Microenvironment

In the same way that a difficult neighbourhood can result in the emergence of criminal elements, a defective stromal microenvironment can trigger and promote the development of cancer cells. This altered microenvironment further protects the tumour against the immune system through fibroblast secretions and other mechanisms. Elimination of cancer cells also requires targeting of the tumour microenvironment to make conditions favourable to normal cells and unfavourable for the malignancy. One such strategy proposed is the use of hypomethylating agents to modify the bone marrow microenvironment in patients with myelodysplastic syndrome.[56]

Cancer-associated fibroblasts

A group of cells that cause this defective tumour environment is the cancer-associated fibroblasts (CAFs). CAFs are known to be derived from tissue-resident fibroblasts[57] that are activated by the tumour microenvironment.[58] CAFs are able to not only promote tumourigenesis,[59] but also cause the tumours to be more difficult to treat and aggressive.[60] This is known to be caused by the release of various substances such as cytokines, growth factors and exosomes, which promote angiogenesis,[59] metastasis[61] and increased resistance against both chemotherapy and radiotherapy.[62] CAFs are also known to exert an immunosuppressive action by preventing the infiltration of CD8+ T cells into the tumour by remodelling the extracellular matrix[63] and promoting tumour vasculature. Reports have shown that the removal of CAFs led to tumour regression with immunogenic tumours,[64] although there are also significant side effects due to the lack of specificity of the treatment,[65] causing damage to surrounding healthy cells. It is therefore crucial to develop a marker specific to CAFs such that these cells can be directly targeted and destroyed while minimising harm to other cells.

Transforming growth factor beta

Transforming Growth Factor Beta (TGFβ) is a cytokine produced mainly by CAFs[66] that modulates processes such as cell invasion, immune regulation and microenvironment.[67] Hence, the malfunctioning of this pathway can lead to the proliferation of cancer cells. When cancer cells lose TGFβ tumour-suppressive responses, they can use TGFβ to their advantage to initiate immune evasion, differentiation into an invasive phenotype, and promote metastasis.[67,68] Galunisertib, a TGFβ inhibitor, was shown in a trial to considerably reduce tumour burden when used alone, and was able to eradicate most metastases and prolong recurrence-free survival even a year after the end of treatment, when it was used alongside anti-PD-L1 therapy.[66] Other trials have also reported synergy between anti-PD-L1 therapy and TGF inhibitors,[69] which makes this treatment strategy very promising.

Radiation Oncology

Radiation therapy is commonly used to treat multiple types of cancer, either alone or together with other cancer therapies, such as surgery, immunotherapy and chemotherapy. For instance, chemotherapy has been commonly used in conjunction with radiotherapy with a curative intent in head and neck[70] as well as lung cancers.[71] Radiotherapy works by directing ionising radiation at the patient's tumour, damaging the DNA of the cancer cells and killing them. However, radiotherapy often results in long-term side effects, such as hypothyroidism,[72] heart disease,[73] facial abnormalities,[74] or even secondary cancers.[75]

Currently, photon beam therapy is the most prevalent form of radiation therapy. Recent technological advancements have helped reduce treatment time,[76] increase the radiation dose conformity and improve accuracy when using photon radiotherapy.[76,77] These advancements enable the tumour to be targeted more specifically, while sparing surrounding tissue, which has undoubtedly contributed to making radiotherapy safer and reducing its side effects.

Recently, a new promising technology that is being explored is proton therapy. Proton therapy works similarly to conventional photon radiotherapy—by delivering ionising radiation to cancer cells and thereby killing them. However, proton therapy has the advantage of greater potential for a higher dose conformity than photon therapy,[78] as it deposits most of its energy over a narrower range.[79] However, proton therapy is limited due to the high costs of building and maintaining proton therapy treatment machinery,[80] and is therefore not widely available. Nevertheless, patients, especially young children, could be spared a life time of more serious side effects of less targeted radiotherapy, conferring potential long-term benefits.[81]

Biology-driven precision radiation oncology could help address the differing biological features of different tumours, which affect their radiosensitivity.[82] However, the discovery of more suitable biomarkers[83] and conducting of more clinical trials[84] must be done to establish its effectiveness, and to explore the possible integration of proton beam therapy with biological knowledge of tumour sensitivity.

Palliative Oncology

Cancer can have a wide range of physical and emotional effects, due not only to severe illness, but also the potential side effects of its treatments. In fact, patients with advanced cancer benefit from early palliative care from interdisciplinary palliative care teams while receiving active treatment.[85] Patients who receive palliative care not only had reduced healthcare costs,[86] but also an improved quality of life, better symptom management,[85] as well as better caregiver outcomes.[87] Results from clinical trials show there is greater benefit from early palliative care referrals as compared to delayed referrals.[88] Hence, it is important for palliative care to be integrated into standard oncological care right from diagnosis, to help meet the needs of both patients and their family members or care givers (Fig. 2).

It is imperative for healthcare professionals who are involved in the care of cancer patients to learn primary palliative care skills,[89] so as to address basic palliative care needs, given the strong evidence that supports palliative care on top of standard oncology care.[90] Palliative care provides much needed support to the patients and their family members, reducing the symptomatic, emotional and devastation brought about by the illness.

Geriatric Oncology

Sixty percent of all cases with cancer and 70% of cancer-related deaths occur in patients aged 65 years and over.[91] It is therefore critical to develop a specific treatment plan for older cancer patients that takes into account their additional needs due to the physiological changes of old age. To accomplish this, a comprehensive geriatric assessment (CGA) should be conducted on all older patients with cancer. CGA can be performed in half an hour[92] and the information from the assessment can be used to tailor the appropriate treatment for the patient, optimise his or her care, and provide important prognostic information. What tools a CGA should comprise still remain largely debatable, but there is a specific set of domains (Fig. 3) that should be part of this

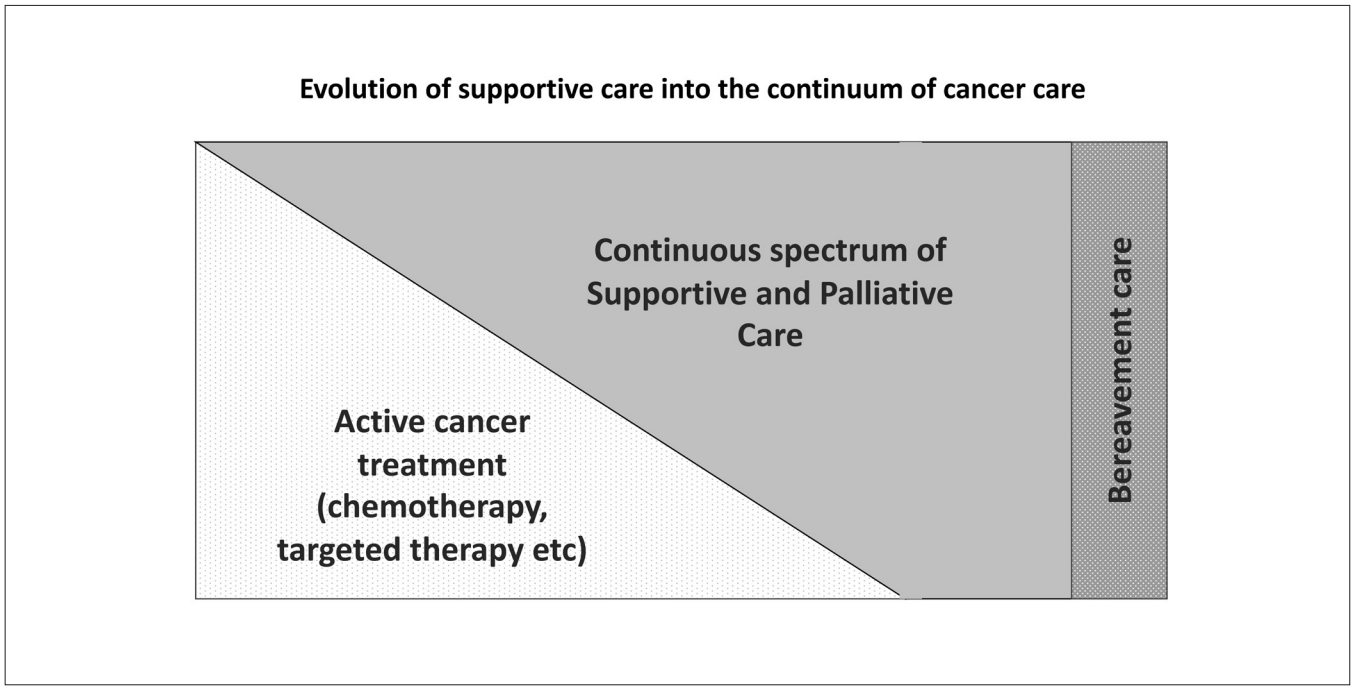

Fig. 2. Evolution of Supportive Care into the Continuum of Cancer Care (where the x-axis represents the time of cancer progression). Supportive and palliative care should be made available to all cancer patients who are undergoing active cancer treatment including after active anticancer treatment is stopped. Palliative care considers the psychological needs of caregivers and therefore helps to ease the transition into bereavement care.

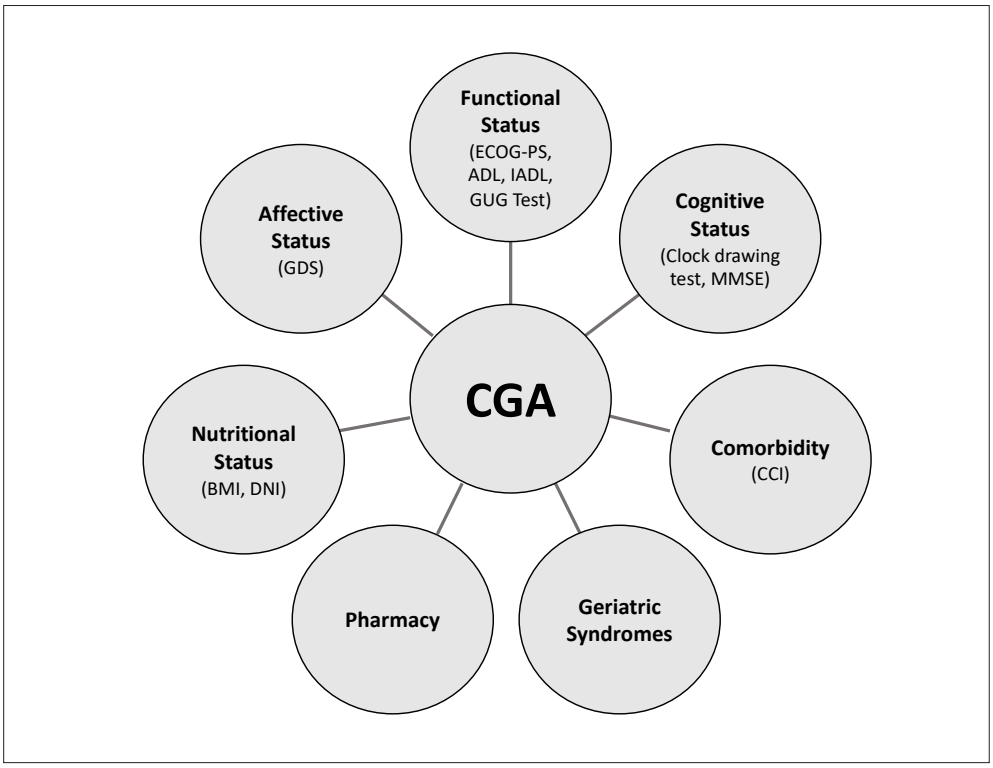

Fig. 3. The key domains that are part of Comprehensive Geriatric Assessments (CGA). CGA can detect problems that are not detected in routine history and physical examinations, due to the tools in this assessment being more specific to the needs of the elderly. The information from the CGA can be used to tailor the appropriate treatment for the patient, optimise their care and provide important prognostic information as well.

assessment, namely functional status, fatigue, comorbidity, cognition, mental health status, social support, nutrition and geriatric syndromes.[93] CGA parameters have been shown to be predictive of the risk of severe treatment-related toxicity[94] and mortality,[95] which may signal to oncologists if there is a need to modify the therapeutic approach to prevent treatment-related complications, such as by providing less aggressive treatment methods. For example, based on the key domains of a comprehensive CGA provided in Figure 3, the physician is able to make recommendations such as the control of blood pressure, discontinuation of specific drugs, or the referral to a dietitian. A Cancer and Aging Research Group chemotoxicity score may also be calculated, as well as make an assessment/prediction of the risk of grade 3 or higher toxicity from chemotherapy. To best utilise the information from the CGA, a multidisciplinary team is needed to address the issues it detects. For instance, patients with cognitive impairment may be referred to a memory clinic, or pharmacists can check for possible drug interactions with medications used to treat other geriatric conditions. The subsequent changes in treatment plan may help to improve overall survival. Given that a significant proportion of cancer patients are older adults, it is evident that the CGA will have an important role to play in the fight against cancer.

Conclusion

Advances in cytotoxic chemotherapy, surgical oncology, genomic medicine, targeted small molecule treatment, cancer immunotherapy and biology-driven precision radiation oncology have resulted in significant improvements in outcomes of cancer treatment, with an increasing number of patients achieving long-term disease control or even being potentially cured. Concurrent advances in palliative care and geriatric oncology have also helped to ensure that patients are managed in a holistic manner by considering their physical, social, psychological and emotional needs in a personalised manner.

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