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Cancer Treatment Adaptation Based on Prognostic and Predictive Biomarkers

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Abstract

Earliest treatment of cancer in the 1800s for patients with localized tumour growths consisted of radical anatomical dissection based on Halstedian concepts of orderly contiguous tumour spread and consideration of cancer as loco-regional disease autonomous of its host.

Keywords: Treatment; Contiguous tumour; Loco-region; Quality of life; Angiogenesis inhibitors; Immunotherapy group

Introduction

In early 1900s, radio-therapy emerged as a modality of cancer cell kill through ionizing radiation that disrupts various pathways of cell cycle. Radiotherapy thus provided an alternative or adjunct modality of loco-regional treatment for various solid tumors. In the past two to three decades, significant technological advances in the conduct of surgery and delivery of radiotherapy have led to more precision in loco-regional treatment, more organ preservation methods, and reduced morbidity. Parallel advances in reconstructive surgeries and various rehabilitation procedures have improved quality of life for patients with early stage solid tumors. Systemic anticancer treatment started with the discovery of cytotoxic chemotherapy in the late 1940s, the first few drugs being nitrogen mustard compounds and anti-foliates used in the treatment of leukemias and lymphomas. Since then, from 1949 to 2014, a total of 150 medicines have been approved including cytotoxic drugs and targeted agents with an indication for at least one type of cancer. Most of the cytotoxic drugs are alkylating agents, anti-microtubule agents, anti-metabolites, and topoisomerase inhibitors which work in different phases of cell cycle, while most of the targeted drugs belong to signal transduction inhibitors, gene expression modulators, apoptosis inducers, hormone therapies, angiogenesis inhibitors, immune modulators, and monoclonal antibodies which targets one or more of the hallmarks of cancer pathogenesis. In the past 5 years from 2015 to 2019, approximately 60 new anticancer medicines, latest being the immunotherapy group of drugs, have been approved and several older drugs are being approved for newer indications, underscoring the steadily escalating efforts in drug discovery and translational cancer research [1]. Additionally, several supportive care drugs used to treat various side effects of cancer therapy as nausea and vomiting, myelo-suppression, febrile neutropenia, gastrointestinal toxicities, neuropathy, and others have developed in parallel, allowing for timely and adequate delivery of intensive treatment protocols. Systemic chemotherapy is administered as cycles or periodic courses, with interval between two doses of an average 3 to 4 weeks, to allow adequate time for normal cells to recover from collateral cytotoxicity [2].

Discussion

Combination therapy with entirely or parentally administered cytotoxic drugs with different mechanisms of action and differing dose limiting toxicities forms the mainstay of treatment of haematological malignancies. Optimization of drug dose, regimen, and schedule over decades through conduct of cooperative group trials have led to significant cure rates in acute leukemias and lymphomas and prolonged progression-free survival in myeloma. Novel cytotoxic drugs, targeted agents, and monoclonal antibodies are used either as single agent or in combination for treatment of relapsed/refractory diseases and for particular indications have moved to the first line therapy [3]. A few targeted agents have changed the treatment paradigm of some diseases, for example, imatinib, a tyrosine kinase inhibitor targeting BCR-ABL, introduced in 2001 in the treatment of chronic myeloid leukemia have obviated the need for upfront allogeneic stem cell transplant in this disease. Similarly, all-trans-retinoic acid and arsenic trioxide targeting and releasing the differentiation block in acute pro-myelocytic leukemia caused by the PML-RARA translocation have resulted in cure rates of 80 to 90% with a chemotherapy-free protocol. In solid tumors, the evolving concept of operable cancer being systemic disease with potential for dissemination through lymphatics and blood stream even in early stages and recognition of complex host–tumour interrelationship affecting disease biology, which were contrary to the old Halstedian principles, led to the experiments for adjuvant systemic therapy in the treatment of localized disease. These experiments of systemic therapy as adjunct to surgery led by Fisher and colleagues in the 1970's, concluded that two paradigms govern the management of cancer, first is related to the use of surgery to eradicate local and regional disease; the second is related to the eradication of systemic disease. The treatment of patients who has no identifiable metastatic disease with systemic adjuvant therapy or neo-adjuvant therapy with either hormonal agents, targeted or cytotoxic chemotherapy, or both have resulted in decreased local and regional recurrences as well as distant metastases after minimal conservative surgery and have improved survival in patients of various solid tumors to the tune of 4 to 15% absolute benefit at different stages [4]. Chemotherapy, along with loco-regional therapy, is also an integral component of curative treatment of certain metastatic solid tumors such as germ cell tumors, chorio-carcinoma, and neuroblastoma, which are highly chemo-sensitive. For most of the other solid tumors with advanced and metastatic disease, systemic chemotherapy and targeted agents are used for palliative treatment. However, with the advent of combination

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chemotherapy, targeted agents, monoclonal antibodies, and immunotherapy, several sequential lines of treatment can be administered safely even for advanced diseases with resultant improvement in clinical outcomes for many of the common malignancies such as breast, prostate, lung, and colorectal cancers. Yet, treatment intent still remains palliative and not curative in majority of metastatic solid tumors, nevertheless, provides better quality of life and considerable prolongation of survival [5]. Multidrug, multiphase combination chemotherapy regimens comprising of cytotoxic drugs, targeted agents, monoclonal antibodies, etc. in defined schedule forms the basis of treatment of haematological cancers. Radiotherapy is generally given for bulky or residual disease sites in lymphoma, for prophylactic or therapeutic cranial irradiation in leukemias, and as single modality radical treatment for plasma-cytoma. Hematopoietic stem cell transplant either autologous or allogeneic is used for consolidation treatment as part of frontline therapy in certain high-risk haematological malignancies, for example, multiple myeloma, Philadelphia positive acute lymphoblastic leukemia in adults, intermediate and high-risk acute myeloid leukemia, and for salvage treatment of refractory/ relapsed haematological cancers. In solid tumors, depending on the stage, all the three main modalities surgery, radiotherapy, and chemotherapy are used in the frontline treatment. Further, hormonal therapy, targeted agents are added to the protocol in certain tumors depending on the biological characteristics and risk group [6]. We will discuss two tumors breast carcinoma and neuroblastoma as prototype for multimodality treatment plan. For stage II/III breast carcinoma, general course of treatment includes neo-adjuvant combination chemotherapy followed by surgery and followed by radiotherapy. Hormonal therapy for duration of 5 to 10 years is added for patients with estrogen or progesterone receptor positive tumors and anti-Her 2 therapy for Her 2 positive tumors. For a subset of very early stage, hormone receptor positive, Her 2 negative tumors, with low recurrence score by molecular tests treatment can be done by only surgery followed by hormonal therapy without the need for radio- or chemotherapy [7]. In high-risk metastatic neuroblastoma, treatment is done with all modalities as combination chemotherapy, surgery, autologous HSCT, radiotherapy, and post-transplant maintenance treatment with differentiation agent and immune modulators. Thus, majority of the malignancies require a multimodality treatment approach for curative outcomes. Treatment decisions are generally taken in a multidisciplinary tumour board consisting of surgeons, anaesthetist, radiation oncologist, and medical oncology experts. Further, the multi-disciplinary team should also consist of nutritionist, physiotherapist, speech therapist, palliative care physicians, infection disease expert, psychosocial counsellors, and other specialists for guiding supportive care during the course of treatment, rehabilitation post treatment, and for monitoring and management of late side effects. In metastatic solid tumors, for most of the common malignancies of lung, breast, prostate, colorectal, renal, ovary, etc., a multitude of treatment options are now available for the first line and subsequent lines of therapy that have resulted in a significant increase in overall survival, up to 12 to 18 months on average over historical outcomes, in particular patient subsets in these cancer subtypes [8]. These treatment options include besides conventional cytotoxic chemotherapy, targeted therapy related to the specific driver genomic alteration, hormonal therapy for hormonally driven cancers, drugs targeting the angiogenesis pathway and tumour microenvironment, and immunotherapy targeting the immune checkpoints involved in tumour cell to immune cell interactions. Current challenge in management of these metastatic solid tumors is in optimizing the right combination and sequencing of treatment. Another important clinical challenge is in evaluating cost effectiveness of the newer drugs for palliative treatment and in identifying futility of further treatment or when to stop further treatment for patients with poor general condition and progressive disease. Other aspects of cancer care such as prevention, screening, early diagnosis, toxicity management, and rehabilitation are important areas, but are beyond the scope of the current review. Discussing the details on each cancer modality and drug, and treatment for individual cancers, is also outside the space of this brief summary [9]. Many comprehensive international guidelines are available that summarizes the treatment approach and algorithm for management of all common malignancies and serve as useful resource. Finally, in clinical practice, treatment decisions require the expertise and experience of the oncology team. Prognostic factor is defined as measurement taken at the time of diagnosis or treatment that is associated with the outcome, determining a patient's ability to fare in the absence of treatment, for example, age of the patient, stage determined by tumour size, nodal involvement and distant spread, grade, cytogenetic or molecular profile, etc. Often a combination of clinical pathological and genetic changes are taken together to determine risk groups and based on the individual risk group treatment can be tailored either intensified for high-risk group patients or de-intensified for low risk [10].

Conclusion

Nonetheless, even cancers impervious to the new drugs could be treated if those malignancies have the right error-riddled DNA signature. In its refined version, the genome of a common bacteriophage and synthetic strands that were designed to fold up its DNA are encapsulated and do not encode any proteins or do any of the normal DNA functions. Potentially, the technique should work on most any form of drug-resistant cancer.

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Conflict of Interest

None

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