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Risks and Future of Cancer Treatment

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Abstract

Predictive factor is a measurement that predicts response or lack of response to a specific treatment. Some common examples include epidermal growth factor receptor (EGFR) mutation in lung cancer that determines response to EGFR inhibitor like gefitinib, Her2/neu amplification in breast cancer that determines response to anti-Her2 therapy like trastuzumab or lapatinib, and K-RAS/N-RAS mutations in colorectal cancer which are a negative predictive factor for response to EGFR monoclonal antibody such as cetuximab.

Keywords: Epidermal growth; Anti-her2 therapy; Antibody; Drugs; Biomarkers; Leukemia

Introduction

Several other biomarkers either in the tumour genome or in germ line deoxyribonucleic acid involving the drug metabolizing pathways are known that can affect responses to particular drugs. A plethora of biomarkers have been studied in different diseases but clinical utility has been established only for a handful of them. With growing understanding of cancer biology and disease pathogenesis, molecular classification is evolving for all cancer types which when clinically validated will help in further prognostication and identification of predictive markers and thereby in personalizing cancer treatment. Treatment results in oncology are generally defined by response rates, disease-free remission, morbidity or late sequel of treatment, quality of life, and survival [1]. In other words, a clinically relevant endpoint is a characteristic that reflects how a patient feels, functions, or survives. In cancer patients, the risk for death from a specific neoplasm is highest in the initial years after diagnosis; it decreases progressively thereafter. To apply the word cured, the time from the cancer diagnosis must be such that the patient's risk of death does not, because of cancer, exceed that of a sex- and age-matched general population [2]. However, in oncology, use of word cure is debatable in view of late and very late relapses in certain malignancies and the more commonly used terminology is long-term survivor. For some of the early stage and good risk malignancies, for example, testicular germ cell tumour, thyroid cancer, Hodgkin's lymphoma, childhood acute lymphoblastic leukemia, and gestational trophoblastic neoplasm, 5- and 10-year disease-free survival is close to 85 to 90% which may be taken as functional cure. For other tumors, available treatment modalities have prolonged survival with a fairly better quality of life making many cancers a chronic disease. On-going translational research in cancer biology and treatment may further help to improve their outcomes [3]. Cancer therapy is a continuously evolving field and every year there is considerable upsurge in new drug discovery and approvals, in drug repurposing and approval of newer indications for older drugs, in newer methods of drug delivery and optimized management of toxicities, in discovery of new predictive biomarkers and new treatment approaches, and also in technological advances in loco regional treatment modalities of surgery and radiotherapy [4].

Discussion

However, there remain several challenges in the path to translational of all these new developments in practice of real precision medicine and into clinically meaningful benefit in cancer survival. Some of the important challenges are dealing with tumour heterogeneity, handling drug resistance either due to pharmacogenomics differences in drug metabolism and transport or more commonly due to acquired mutations/alterations in cancer genome or its downstream pathway, finding of actionable alterations in the tumour tissue or its microenvironment, and identification and validation of predictive markers of immune therapy [5]. Also, the disconcerting background of genomic variability creates issues regarding clinical interpretation, application, and validation of enormous and complex genomic data. Another practical challenge is in finding the optimal combination regimen, targeting several molecular alterations concurrently or in precise sequence, and validating them in clinical trials for demonstrating final benefit in survival. Some of the additional challenges pertaining to resource-limited settings in the Indian context are wide disparity in the access to cancer treatment, delayed presentation with higher disease burden, heterogeneity in resources, available expertise and treatment cost and payment structure across centres, poor social support system, significant financial constraints as most of the treatment expenses are met out of pocket, poor understanding of the disease and its treatment course and consequently higher treatment abandonment rates, restrictive access, non-availability or prohibitive cost of the latest anticancer drugs, and very low rates of recruitment into well-designed clinical trials. Besides development of newer generations of older targeted agents, discovery of new drugs targeting single molecular abnormality or pathway, and the expanding field of immune checkpoint inhibitors, the following novel approaches to cancer treatment which have already been studied in early phase clinical trials are making headway into mainstream therapy [6]. These include cellular immune therapy such as CAR-T cell therapy, anticancer vaccines, and new therapeutic approaches based on genomic editing. Also, so far the approach to cancer treatment had been reductionist, which is targeting single molecular abnormality or cancer pathway that has modestly improved outcomes, but to move toward potential cure, systems biology or multipronged approach targeting several driver molecular pathways or cancer hallmarks of etio pathogenesis simultaneously might be a promising therapeutic strategy. As mentioned above, challenge for this

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approach is in optimizing the right combination or sequence, and in finding valid biomarkers; however, with better comprehension of next-generation precision oncology tools and data this should be attainable in the near future. Further, to find answer to locally relevant clinical problems in the Indian context, well-designed clinical trials through multi-centre collaboration at the regional or national level is a pressing need that would be vital to improve outcomes close to that seen in the western developed world. In this concise review, we have attempted to outline the major modalities of treatment in oncology, their evolution in brief, recent advances and challenges, and multimodality approach to cancer management in clinical practice with some common examples [7]. Overall, treatment has to be evidence-and value-based, cost effective, and guided by local problems, expertise, and resources. We hope this would be a useful summary on cancer therapy for a new induct into oncology or for anybody who is keen on understanding the basic principles of cancer treatment, and encourage them to read and explore further and contribute their bit to cancer management. Modern cancer treatment has evolved over several years to reach the current era of precision therapy [8]. Exciting developments in all modalities of cancer treatment and rapidly growing arena of translational research are contributing to the steady improvement in clinical outcomes. Although several old and new challenges have to be overcome, parallel technological advances in the tools and techniques of drug discovery has promise for future. History of modern cancer treatment dates back to about 200 years, although cancer is as old as humankind or even life. The incidence rate for all cancers in all age groups combined is progressively rising, from 182.3 per 100,000 in 2012 to 197.9 per 100,000 in 2018 globally. Nevertheless, mortality rates overall have been marginally but steadily declining over the past few decades, from 102.4 per 100,000 in 2012 to 101.1 per 100,000 in 2018.4 GLOBOCAN 2018 estimated an incidence of 18.1 million new cancer cases and 9.6 million cancer deaths worldwide for 2018 [9]. Growing understanding of cancer biology, parallel advances in diagnosis and risk stratification, improved cancer treatment modalities, new drug discoveries and better supportive care, and cooperative group trials, all have resulted in significant rise of survival for both childhood and adult cancers. In this very brief review on cancer therapy, we attempt to summarize the principles of cancer treatment and their application and challenges in clinical practice for the beginners in oncology. Cancer is broadly divided into solid tumors and haematological malignancies. The intent of cancer therapy may be curative or palliative depending on the disease and patient characteristics. Solid tumors of different organs are generally staged as localized, loco-regional, or metastatic disease. Localized and regional solid tumors are primarily treated with loco-regional treatment modalities, like surgery and radiotherapy. Also, depending on the stage and disease extent, systemic chemotherapy is added as adjunct to local treatment to prevent recurrences and thereby improve survival. Metastatic solid tumors and all haematological malignancies are principally treated with systemic chemotherapy. Loco-regional treatment with surgery or radiotherapy is also considered for certain metastatic solid tumors and haematological malignancies as component of main treatment plan or for palliation [10]. Other components of systemic therapy include hormone therapy, various targeted agents, monoclonal antibodies, and immunotherapy which are used in the course of treatment of different solid and haematological malignancies. Thus, treatment of cancer generally requires multimodality approach which has to be tailored as per the cancer type, stage, and biology, and according to the patient's clinical risk group and demographic characteristics. Loco-regional treatment modalities such as surgery and radiotherapy are used to treat early stage solid tumors. Systemic therapy such as cytotoxic chemotherapy, hormone therapy, targeted drugs, and immunotherapy are used alone or in different combinations to treat haematological malignancies, as adjunct therapy for early or locally advanced solid tumors and as palliative therapy for metastatic solid tumors. Hematopoietic stem cell transplant is used for various indications in the treatment of haematological malignancies. Advances in supportive care have supplemented the administration of all these intense treatment modalities.

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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