EDITORIAL

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By 2022, Cancer is Now a More Chronic Disease with Chronic Difficulties to Go Along with It

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ABSTRACT Cancer is a disease in which some body cells with genetic or epigenetic changes become capable of replicating and invading other regions of the body uncontrollably. Numerous functional abilities and features are acquired by these cells during this multistage neoplastic process. In the last 20 years, many agents have been discovered and used in the fight against cancer. However, the use of these drugs in appropriate patient groups is still a serious problem. Many cancer types are on the way to becoming chronic diseases; conscientious physicians who are unable to provide appropriate treatment due to economic factors and other reasons face an additional burden.

Keywords: Cancer; chronic disease; novel drugs

Cancer is a disease in which some body cells with genetic or epigenetic changes become capable of replicating and invading other regions of the body uncontrollably. Numerous functional abilities and features are acquired by these cells during this multistage neoplastic process. In the "hallmarks of cancer", the role of these acquired characteristics in carcinogenesis is studied. The hallmarks of cancer help to distill the complexity of cancer into an increasingly logical analysis. This is crucial to understand the unknown aspects of carcinogenesis and to integrate that knowledge into cancer treatment strategies. Hannahan and Weinberg updated the hallmarks of cancer in 2010; however, the developments in the past 11 years have shown that additional mechanisms are involved in tumor biology and pathogenesis. Now, we have gained clarity regarding the features of cancerous cells and the mechanisms involved, which can help with further analysis. The emergence of new treatment options for cancer, along with the identification of 4 new mechanisms involved in cancer, has made cancer chronic both in the early and advanced stages. The proportion of patients with various cancer subtypes getting cured has increased, and survival rates have increased even in patients with advanced-stage cancer. Although this had positive effects on all aspects of cancer, the number of patients with cancer in society and the costs of continuous treatments have increased the burden on health and insurance systems. Additionally, the in-

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ability to provide effective treatment modalities for various reasons creates administrative and conscientious burdens on medical oncologists.

Here, we discuss the newly identified pathways of cancer in the year 2022 and the treatments that were proved effective at the administrative stage.

Currently, the eight hallmarks of cancer are acquired capabilities for sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction. In 2022, 4 new functional characteristics were defined in the hallmarks of cancer, namely unlocking phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and senescent cells.[1]

The importance of cancer differentiation into stages was known. Three subclasses of phenotypic plasticity are dedifferentiation, blocked differentiation, and transdifferentiation. These subclasses of phenotypic plasticity are apparently effective in multiple cancer types at various stages of progression and/or response to therapy. The proposition was made that unlocking cellular plasticity to enable various forms of disrupted differentiation constitutes a discrete hallmark capability, distinguishable in regulation and cellular phenotype from the well-validated core hallmarks of cancer.[2]

An apparently independent mode of genome reprogramming that involves purely epigenetically regulated changes in gene expression might be termed nonmutational epigenetic reprogramming. The 2022 version of the hallmarks of cancer discusses purely epigenetically regulated changes in gene expression, such as microenvironmental mechanisms of epigenetic reprogramming, epigenetic regulatory heterogeneity, and epigenetic regulation of the stromal cell types populating the tumor microenvironment. The role of the tumor microenvironment in carcinogenesis is indisputably known. Aberrant physical properties of the tumor microenvironment may cause broad changes in the epigenome and distinctive changes in the phenotype, which can cause the clonal growth of cancer cells. Thus, it is one of the new functional dimensions of hallmark capabilities. Epithelial-mesenchymal transition and hypoxia are crucial epigenetic regulatory mechanisms. Additionally, cancer-associated fibroblasts, innate immune cells, endothelial cells, and pericytes attract attention as microenvironment components influencing new hallmark capabilities. Single-cell multi-omics profiling technologies and nonmutational epigenetic reprogramming have been proved to be integrally involved in enabling the provisional new hallmark capability.[3-5]

Resident bacteria and fungi (microbiomes) called microbiota are symbiotically associated with the body's barrier tissues. A growing understanding of its effects on health and disease has made it a topic of increasing importance because of the detection of microbial species with next-generation sequencing (NGS) and bioinformatics technologies. Growing evidence suggests that polymorphic variability in microbiomes between individuals can profoundly affect cancer phenotypes. The modulatory roles of the microbiota on carcinogenesis were identified through different mechanisms. Additionally, microbiomes may affect cancer pathogenesis and response to therapy in other organs (e.g., cholangiocarcinoma). Furthermore, the intratumoral microbiota is an interesting entity with a role in carcinogenesis.[6-8]

Cell aging is caused by nutrient deprivation, DNA damage, damage to cellular infrastructure, and imbalances in cellular signaling networks. Senescent cells, which represent cellular aging (irreversible), play a role in carcinogenesis. Although it is a protective mechanism against neoplasia, it can stimulate neoplastic development through different mechanisms, and it particularly affects the microenvironment with its secretory properties.[9,10]

Integration of new functional capabilities into the hallmarks of cancer will allow a better understanding of their role in carcinogenesis steps and comprehensive tumor identification.

Undoubtedly, mankind has made significant progress in the fight against cancer in the past half a century, but life-saving developments have begun to emerge continually in the past 15 years.

NEUROTROPHIC TYROSINE RECEPTOR KINASE INHIBITORS

Neurotrophic tyrosine receptor kinase (NTRK) inhibitors were one of the targets that were moved from translational oncology to medical oncology with personalized treatments. Although it appears to be intense in certain cancers (such as secretory breast cancer in adults, salivary gland tumors, infantile fibrosarcoma in childhood, and gliomas) and rarely found in other cancers (such as thyroid cancer, lung cancer, colon cancer, melanoma, other subtypes of sarcomas, etc.), it appeals to numerous patients with several cancer subtypes.

These fusions, whose investigations are recommended in patients having cancers without other driver mutations, can be examined through immunohistochemistry, fluorescence in situ hybridization, real-time polymerase chain reaction, and NGS. NGS is the most recommended among these methods.[11] The first-generation NTRK inhibitors are entrectinib and larotrectinib, of which laroctenib is more TRK receptor-specific. In phase 1 and 2 studies, objective response rate (ORR) rates were 60%-70%, and larotrectinib-related DoR time was 35.2 months.[12,13] Efficacy was found to be independent of the histological subtype, and the group with cranial metastases had similar efficacy. The side effects of these agents, which have a lower side-effect profile than do other tyrosine kinases, are manageable, and this is also reflected in drug withdrawal rates. Resistance to these agents can develop as on-target or off-target. In the case of on-target resistance, second-generation agents (such as selitrectinib, repotrectinib, and taletrectinib) can be used. For off-target resistance, the agents of secondary mutations (such as KRAS, MET, BRAF, and IGF1R) can be used. The use of these drugs until disease progression or until unmanageable side-effect development may not be cost-effective. The monthly treatment cost for only first-generation agents varies between $11,000 and $17,000.

POLY-ADP RIBOSE POLYMERASE INHIBITORS

In 2009, Fong et al. published a preliminary study on poly-ADP ribose polymerase (PARP) inhibitors, which consisted of 60 patients with various cancers with BRCA mutations, including ovarian, prostate, breast, sarcoma, and melanoma. Among the 60 patients, 22 patients were BRCA carriers and showed 63% clinical response to olaparib treatment.[14] Later, many studies have been conducted to determine the efficacy of PARP inhibitors in several cancer types. In ovarian cancer, olaparib, niraparib, and rucaparib were found to significantly prolong progression-free survival (PFS) rates based on platin response in epithelial ovarian cancer in SOLO-2, PROMA/ENGOT-OV26, and ARIEL-3 phase trials, respectively. Conversely, PARP inhibitors showed positive results and prolonged PFS in patients with non-BRCA mutant ovarian cancers.[15] PARP inhibitors are effective in the treatment of BRCA mutant, non-BRCA mutant, and homologous recombination deficiency groups and are under investigation to assess their effectiveness in combination with immunotherapies. MEDOLIA phase 2 trial tested durvalumab with olaparib and showed 72% ORR and 11 months of PFS in platin-sensitive recurrent ovarian cancers.[16] PARP is being studied in early breast cancer, in novel combinations, and in patients with somatic BRCA mutations and other *HRR* gene alterations who do not have inherited BRCA mutations. PARP inhibitors, in combination with immune checkpoint inhibitors, are now being studied in phase 2/3 trials for the treatment of triple-negative breast cancer (TNBC).[17] OlympiAD and EMBRACA phase 3 trials showed that olaparib and talazoparib significantly increase PFS duration by approximately 3 months compared with standard chemotherapy (CT). Lastly, the Food and Drug Administration (FDA) approved rucaparib and olaparib for prostate cancer treatment in May 2020 and olaparib for pancreatic cancer treatment. All these studies have promising results, and the indications will be expanded to other cancer types in the future.

DRUG-ANTIBODY CONJUGATES

Drug-antibody conjugates (ADC) are produced through a combination of a receptor-specific monoclonal antibody and a cytotoxic chemotherapeutic agent.[18] The first clinical trial of cancer treatment with ADCs was conducted in the 1980s, but ADCs were not being used in clinical treatment due to their

toxicity.[18] In 2013, trastuzumab emtansine (TDM-1) became the first FDA-approved ADC for breast cancer treatment. TDM-1 contributed to survival in trastuzumab-refractory advanced Her2-positive breast cancer.[18] In 2019, fam-trastuzumab deruxtecan (T-Dxd) became the second FDA-approved ADC, with proven efficacy in patients with breast cancer who have taken at least 2 lines of anti-Her2 agents.[19] The DESTINY Breast-03 study demonstrated the superiority of T-Dxd in terms of PFS over TDM-1, which was the standard treatment for Her2-positive advanced breast cancer (HR:0.28).[19] A study comparing T-Dxd with the pertuzumab-trastuzumab-taxane combination in the first line is warranted. An important new concept that arose with the use of T-Dxd and trastuzumab-duocarmazine (T-Duo) in breast cancer was the "Her2-low" disease.[20] In the phase 1b study conducted on patients with Her-2 low advanced breast cancer, the ORR with T-Dxd was 37%, and the duration of response was 10.4 months.[20] In the phase 1b study investigating the efficacy of T-Duo, the ORR was 28% in patients with hormone receptor (HR) positive Her2-low breast cancer and 40% in those with triple-negative Her2-low.[20] In the phase 3 study involving patients with advanced Her2-low breast cancer, T-Dxd was superior to standard therapy in terms of both PFS and overall survival (OS).[21] Therefore, the Her2-low concept is crucial in the molecular classification of breast cancer. Another practice-changing ADC in advanced TNBC was sacituzumab-govitecan (SG). The efficacy of SG against physician chosen single-agent CT (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with advanced-stage TNBC who received at least 2 lines of therapy (at least one of them in the metastatic setup) was investigated in a phase 3 study.[22] Median PFS values in the SG and control arms were 5.6 and 1.7 months, respectively (HR:0.52).[22] Thus, SG became the first ADC to receive FDA approval for advanced TNBC treatment. Moreover, ADCs were effective against bladder cancer. In EV-301, a phase 3 study, enfortumab vedotin (EV) was compared with physician-selected single-agent CT (docetaxel, paclitaxel, or vinflunine) in patients who had disease progression with platinum-based CT and immunotherapy.[23] Median OS was 12.88 months in the EV arm and 8.97 months in the CT arm (HR:0.70).[23] On the basis of these OS data, EV was approved by the FDA for bladder cancer treatment. In phase 2 TROPHY-U-01 study, an ORR of 27% was obtained with SG in patients with advanced bladder cancer who had failed platinum-based CT and immunotherapy.[24] Therefore, SG also received FDA approval for the treatment of advanced bladder cancer. ADCs are used frequently in many cancer types. As expected, drug-related toxicities may also occur. However, ADCs currently approved by the FDA are generally tolerable. However, many patients cannot access ADCs like other newly produced drugs due to their high cost and reimbursement barriers.

IMMUNOTHERAPY

Immunotherapy involves the use of specific components of a person's immune system to fight diseases. The fields of immunology and oncology have been linked since the late 19th century, when surgeon William Coley reported that an injection of killed bacteria into sarcoma sites could lead to tumor shrinkage.[25] Since then, the understanding of the correlation between immune surveillance and tumor growth has advanced exponentially, which has led to broad therapeutic advances that are now being studied in all cancer types. Immune checkpoint inhibitor therapies are now widely indicated in numerous cancer types. Because of prolonged OS in phase 3 trials and durable responses in phase 1 and 2 studies, antibodies inhibiting programmed cell death protein 1 (PD-1; pembrolizumab, nivolumab, dostarlimab) and programmed death-ligand 1 (PD-L1; atezolizumab, avelumab, durvalumab) were approved for numerous clinical indications and are being evaluated in multiple other malignancies.[26] Furthermore, anti-CTLA4 antibodies (ipilimumab and tremelimumab) were approved for monotherapy or in combination with anti-PD-1/PD-L1 antibodies in various cancer types.[27] An increased understanding of underlying immunologic mechanisms is leading to the identification of several additional potential targets for checkpoint inhibition. Some of the potential targets are CD137, OX40, GITR, ICOS, CD40, CD28, CD47, LAG3, and TIM-3. Furthermore, vaccines, oncolytic viruses, CD3-directed therapies, chimeric antigen receptors, and *ex vivo* expansion of tumor-infiltrating lymphocytes are other strategies for cancer immunotherapy.[28]

The literature on cancer immunotherapy is developing day by day. This increases the prospective treatment of patients with cancer, but the difficulty of accessing medicines, difficulties in reimbursements, and financial toxicity risk are also increasing every day.

In conclusion, the economic burden of these drugs will be one of the most important disadvantages, particularly in developing countries. The quality of life and cost-effectiveness analyses of these drugs must be performed, and the expenses involved in the use of these drugs must be reimbursed by insurance systems to prescribe them in clinical routine. This situation puts medical oncologists who have adopted the principle of giving the best treatment to their patients at a dead end. Many cancer types are on the way to becoming chronic diseases; conscientious physicians who are unable to provide appropriate treatment due to economic factors and other reasons face an additional burden.

Informing

Due to the presence of the name of the journal editor's among the authors, the assessment process of the study was conducted by the guest editor.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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