EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 12
391-407
Year: 2021

IMMUNOTHERAPY IN DIFFERENT CANCERS

***Mallam Meghana Goud and Dr. Hajeera Fathima**

Pharm D. 4th Year Joginpally B. R. Pharmacy College Moinabad.

***Corresponding Author: Mallam Meghana Goud**
Pharm D. 4th Year Joginpally B. R. Pharmacy College Moinabad.

Article Received on 17/10/2021 **Article Revised on 07/11/2021** **Article Accepted on 27/11/2021**

ABSTRACT
Patients' survival and quality of life have improved significantly as a result of cancer immunotherapy. Immunotherapy has firmly established itself as a novel pillar of cancer care in a variety of cancer types, from the metastatic stage to adjuvant and neoadjuvant settings. We show how the history of cancer immunotherapy paved the path for discoveries that are today considered standard of care in this review paper. We also discuss the present drawbacks and limitations of cancer checkpoint immunotherapy, as well as how cutting-edge research in the fields of tailored cancer vaccines, autoimmunity, the microbiome, the tumour microenvironment, and metabolomics is attempting to address these issues in different cancers like metastatic colorectal cancer, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, and graft versus host disease. Cancer immunotherapy employs a variety of ways to boost tumour immunity and marks a paradigm shift in cancer treatment, as attention has shifted from the tumor's origin place to its "biologic passport." Biologic modifiers like cytokines and vaccines, adoptive cell therapies, oncolytic viruses, and antibodies against immune checkpoint inhibitors like the co-inhibitory T-cell receptor PD-1 and one of its ligands, programmed death-ligand 1, are among the various types of cancer immunotherapies discussed here.

KEYWORDS: immune system, adoptive cell therapy, immune checkpoint inhibitors, allogenic stem cell transplantation, haematopoietic stem cell transplantation, immunotherapy.

INTRODUCTION
In the treatment of cancer patients, the field of immuno-oncology has proven revolutionary. In the late 1800s, William B. Coley, now widely regarded as the father of immunotherapy, attempted to harness the immune system's capacity to cure cancer for the first time. As an orthopaedic surgeon who operated on patients with bone sarcomas, he found that certain patients who had major postoperative wound infections—a common occurrence when aseptic technique wasn't yet perfected—would have their unresected tumours spontaneously shrink. Coley began injecting live and inactivated germs such as Streptococcus pyogenes and Serratia marcescens into over a thousand patients in 1891.[1]

marcescens in the hopes of causing sepsis and eliciting powerful immunological and antitumor responses. His bacterium combination became known as "Coley's toxin" and is the world's first reported active cancer immunotherapy intervention. Coley obtained long-term full remissions in sarcoma, lymphoma, and testicular carcinoma, among other cancers. However, early in the twentieth century, oncologists adopted surgery and radiotherapy as alternative conventional therapies due to the lack of a recognised mechanism of action for Coley's toxin and the risks of purposefully infecting cancer patients with dangerous germs.[1]

Cancer immunotherapy (CI) is fast progressing, and it is currently regarded as the "fifth pillar" of cancer treatment, alongside surgery, cytotoxic chemotherapy, radiation, and targeted therapy. Antibodies targeting inhibitory immune checkpoint molecules are the CI that has aroused the greatest research. Despite the fact that they have only shown dramatic effects in a small fraction of malignancies so far, it's tough not to get thrilled about their potential. In a recent meta-analysis of ipilimumab, a monoclonal antibody that targets CTLA-4, a type of immune checkpoint receptor or negative regulator of T-cell immune function, more than 20% of patients Patients with metastatic melanoma who had a single round of treatment survived for ten years with no signs of disease. The 10-year survival rate before this treatment was less than 10%. Combination therapy with another immunotherapeutic agent has even more promise, as seen by a 50% response rate in metastatic melanoma when another checkpoint inhibitor antibody, nivolumab, a monoclonal antibody (mAb) that targets the PD-1 receptor on T-cells, was added. CI has also been found to be helpful in other types of cancers, and its use in

combination with other therapeutic modalities (immuno-oncology) has demonstrated to be quite beneficial.[2]

Immunotherapy has been a significant aspect of the treatment of several cancers in recent decades. Immunotherapy has proven to be an effective treatment for cancer patients alone or in combination with other treatments such as surgery, chemotherapy, and radiation therapy by either strengthening the host immune responses against tumours, supplying modified immune system components, or counteracting signals produced by cancer cells that suppress immune responses. As our knowledge of the immune system grows, more small compounds, peptides, recombinant antibodies, vaccines, and cellular therapy modalities are being used to control the immune response for cancer treatment.[3]

IMMUNE CHECKPOINTS

Several signaling pathways negative regulators of T cell activation act as 'checkpoint molecules,' allowing the immune response to be fine-tuned and hyperactivation to be controlled. The most effective T cell immunological checkpoint molecules are cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1). They have biological effects in different parts of the body and at different times during the T cell's lifespan8. As a result, they functionally complement each other, ensuring that T cell responses maintain self-tolerance while efficiently safeguarding the body against infections and neoplasia. Several pioneering research groups have successfully targeted CTLA4 and PD1 as therapies for a variety of diseases.[4]

IMMUNE CHECKPOINT INHIBHITORS

T-cell activity is suppressed by immune checkpoint proteins such as PD-1 and CTLA-4, which begin signalling pathways. CTLA-4 is found on the surface of CD4- and CD8-positive lymphocytes and competes with the T-cell–costimulatory receptor CD28 for binding to T-cell–costimulatory factors, which are found on the surface of antigen-presenting cells in the early stages of the immune response. CTLA-4 binding inhibits the generation of IL-2 and T-cell proliferation. PD-1 is a cell-surface receptor that binds to the ligands PD-L1 and PD-L2 and is found on a variety of immune cell types, including T cells, B cells, and NK cells. PD-L1 is found in a variety of tissues, including tumour cells.[5]

PD-L2 is predominantly expressed on hematopoietic cells. IFN- generated by activated T and NK cells stimulates PD-L1 expression. In peripheral tissues, PD-1 signalling suppresses previously activated T lymphocytes. To allow self-tolerance, CTLA-4 and PD-1 signalling are closely regulated; nevertheless, tumour cells can exploit these pathways, including checkpoint protein signalling, to evade the immune response and produce a microenvironment that allows tumour growth. T-cell exhaustion is characterised by diminished T-cell effector function and proliferation, and is caused by tumour cells upregulating the PD-1 pathway.[5]

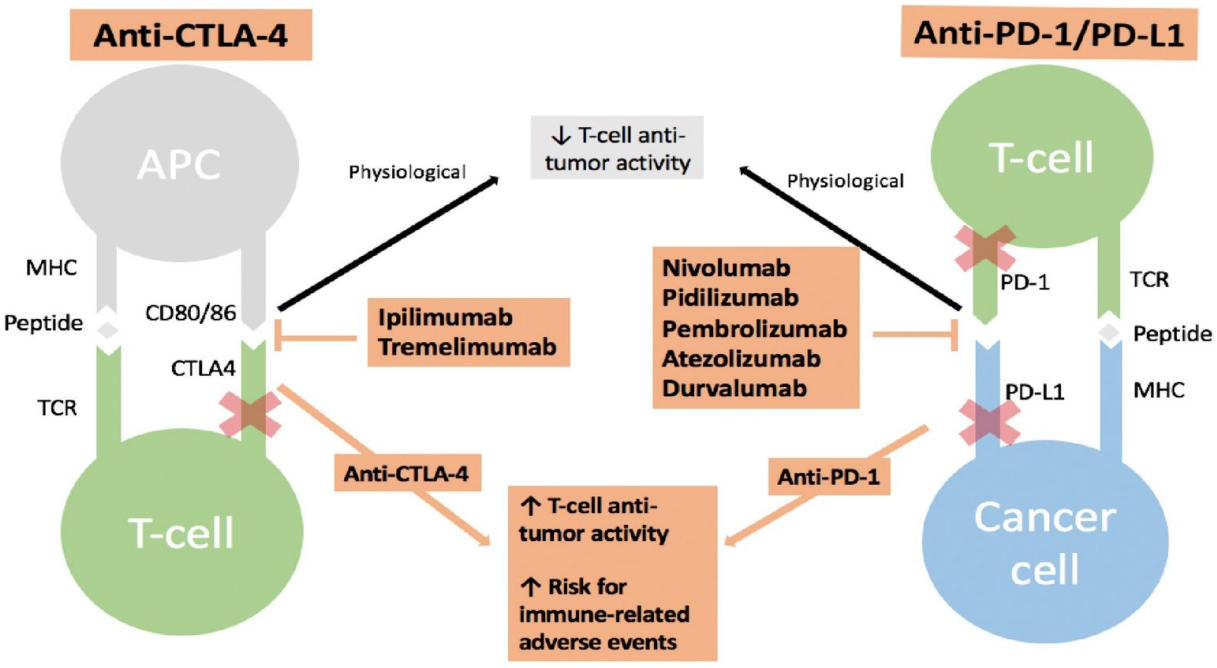


Figure 1.

The biological function of PD1/PDL1

PD1 was first discovered in 1992 as a potential apoptotic mediator, but further data revealed it may also play a role in immune system hyperactivation, similar to CTLA4[6] PD1 shares 20% and 15% amino acid similarity with CTLA4 and CD28, respectively, as a type 1 transmembrane glycoprotein in the immunoglobulin superfamily.[6,7]

Human PD1 is produced on T cells in response to TCR stimulation and binds to the B7 homologues PDL1 (also known as B7-H1) and PDL2 (also known as B7-DC),

which are prevalent in non-haematopoietic tissues and can be activated by pro-inflammatory cytokines.[8,9,10]

When the mouse PD1 orthologue, Pdcd1, was shown to produce autoimmunity in vivo, the main involvement of the PD1 axis in the negative control of T cell activation became obvious in 1999. Splenomegaly developed in C57BL/6 mice missing a functioning PD1 protein.[11] These mice developed moderate T cell-mediated lupus-like glomerulonephritis and arthritis as they aged, which was aggravated by Fas gene lpr mutations.[12] Additional mouse strains were studied, and it was shown that Pdcd1–/– animals of the BALB/c strain had cardiac inflammation that led to dilated cardiomyopathy.[13] In comparison to their Pdcd1-sufficient counterparts, non-obese diabeticPdcd1–/– mice developed accelerated type 1 diabetes mellitus.[13]

Blocking PD1/PDL1 in cancer

Following the finding that the PD1 axis is involved in T cell negative regulation, preclinical research looked into whether inhibitors of this system may be employed for cancer treatment and biomarker development. First, it was discovered that overexpression of PDL1 or PDL2 in cancer cell lines inhibited the CD8+ T cell cytotoxic antitumor response, whereas tumours were rejected in mice lacking functional PD1.Second, blocking PD1 inhibited the development of myeloma cells implanted into syngeneic animals.[13] In syngeneic mice, however, transplanted cells overexpressing PDL1 or PDL2 resulted in enhanced tumour colonisation, burden, and invasiveness.[13] Using mAbs, or secreted PD1 extracellular domains to block the PD1 axis restored these effects and increased T cell cytotoxicity against tumour cells.[14,15]

In animal models, PD1 inhibition enhances antitumour immunity while simultaneously limiting haematogenous seeding of B16 melanoma and CT26 colon cancer metastases.[16] As a result, PD1/PDL1 suppression can improve tumour cytolysis while also limiting metastasis. Apart from the involvement of PD1 and its ligands in cancer treatment, several studies have found a negative association between the expression of proteins involved in the PD1 axis in human tumours and prognosis, implying that these proteins could be used as biomarkers.[17,18,19]

ADAPTIVE T CELL TRANSFER THERAPY

T-cell adoption is a type of T-cell therapy that involves the transfer of T cells from Adoptive T cell (ATC) treatment, which involves injecting autologous or allogenic T cells into cancer patients, has shown a lot of promise in recent years. Southam et al. proved the viability of this sort of therapy in 1966, when half of the patients with advanced cancer showed tumour regression after co-transplantation with patient-derived leukocytes and autologous tumour cells.[20] Clinical benefit was found to be mediated by a T cell graft versus tumour response[21] in allogenic haematopoietic stem cell transplantation for leukaemia, which were the first effective adoptive transfer technique utilised clinically.

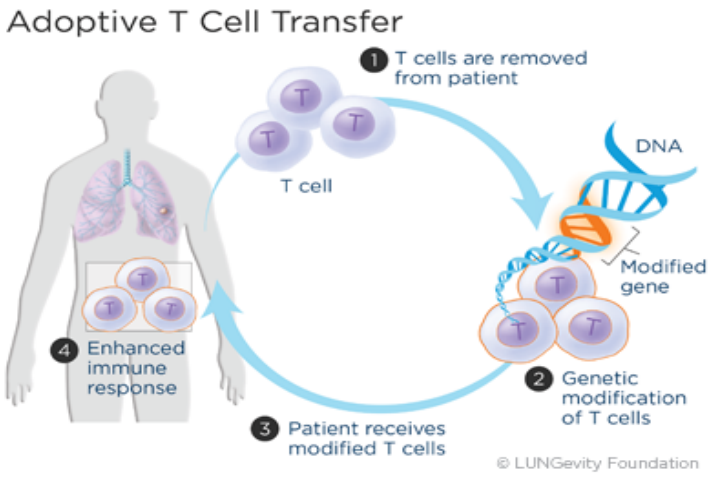


Figure 2.

The National Cancer Institute pioneered ATC therapy using tumor-infiltrating lymphocytes (TILs) for the treatment of metastatic melanoma in the late 1980s.[22] Lymphocytes obtained from a cancer biopsy were considerably enlarged with IL-2 before being reinfused intravenously with a big bolus of IL-2 into the same patient. The objective response rate was 34%, however the median response time was just 4 months, and only a few patients had a complete response.[23]

Later investigations in 93 patients with metastatic melanoma that included lymphodepletion before ATC therapy were more successful, with total tumour regression in 20 (22 percent) patients, 19 of whom were still in complete remission 3 years following treatment.[24] High-throughput technology enabled the screening and enrichment for neoantigen-specific TILs, which showed promise in a patient with metastatic breast cancer.[25] Furthermore, knocking down the gene encoding cytokine-inducible SH2-containing protein

(Cish), a negative regulator of TCR signalling, was shown in mice models to improve the antitumour response to ATC therapy.[26]

TIL-based ATC therapy, on the other hand, requires the presence of effector T cells with antitumour activity in the tumour, which is not the case for many cancer types. Other novel techniques of tinkering with T cell activity and proliferation may open the door to a wider range of treatments.[27]

ATCs' limitations and negative impacts

Toxicities from CAR T cell therapy can impact a variety of organ systems and have varying degrees of severity.[28] Cytokine release syndrome (CRS) and neurotoxicity are the most common side effects in patients.[29] CRS is caused by CAR T cells' high activation and proliferation in vivo, and it usually manifests soon after cell transplantation. Hypotension, high temperature, capillary leakage, coagulopathy, and multisystem organ failure are common symptoms, but they can also be severe and life-threatening.

Serious neurological events, such as CAR T cell-related encephalopathy syndrome, might occur. This illness is marked by disorientation and delirium, but can also include seizures and cerebral oedema.[29] For milder types of CRS and CAR T cell-related encephalopathy syndrome, glucocorticoids are the first-line treatment. Tocilizumab, a humanised anti-IL-6 antibody, is a promising second-line treatment for CRS induced by CAR T cell therapy.[30]

The processes causing these adverse effects are unknown, but more research could lead to solutions to avoid or reduce toxicity. CRS is not driven by CAR T cell-derived IL-6, but rather by recipient macrophages that release IL-6, IL-1, and nitric oxide, according to a new mouse model developed recently. As a result, IL-1 blockage could be a promising new weapon in the arsenal against CRS.[31] Furthermore, a clinical trial employing CD19-specific CAR T cells with limited affinity showed lower toxicity and improved efficacy.[32] Engineering CAR T cells with multiple receptor specificities[33] and reducing the half-life of cellular toxicity by using mRNA-based methods that allow for transient receptor expression[34] or including suicide cassettes that can be activated by exogenous agents to clonally delete the infused cells are two additional efforts to reduce toxicity.[34]

The ATC technique involves a patient-specific therapy design, can be prohibitively expensive, has restricted patient access, and is difficult to manufacture. The CAR T cell treatments cost US$475,000 and US$373,000 per patient, respectively, in the United States.[35] These figures do not include the additional expenditures of treating the severe side effects that are frequent with CAR T cell therapy, which are expected to boost drug-related costs by US$30,000 or more.[35] Checkpoint blocking is more expensive than CAR T cell treatment, costing over $12,500 each month.[36]

Patient access to CAR T cell therapies is also a serious issue, as only a few laboratories have been certified to create CAR T cells, and only a few specialised tertiary care centres have been approved to give this therapy.[37] Finally, variations in CAR T cell manufacture and a lack of consistent processes can lead to a wide range of results.[37]

IMMUNOTHERAPY IN METASTATIC COLORECTAL CANCER

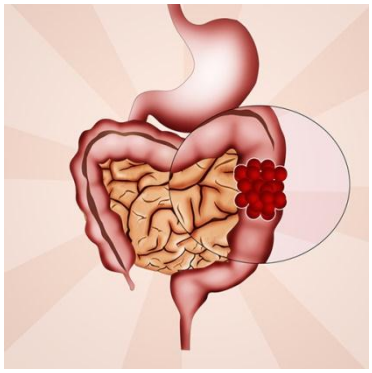


Figure 3.

Colorectal cancer (CRC) remains the second biggest cause of cancer death, accounting for 8.3% of all cancer-related deaths each year and around 140,250 new cases identified in 2018.[38] Although overall CRC mortality is decreasing, advanced disease survival is still low.[39,40] For the past two decades, chemotherapy has been the primary therapeutic option, and with the introduction of tailored monoclonal antibodies, survival rates have begun to rise even more.[41]

Immunotherapy, on the other hand, has been the most intriguing paradigm shift in cancer treatment in recent years.[42,43] It has become the standard of care for a variety of different cancers since it was first approved for the treatment of melanoma.[44] Immunotherapy has also shown promise in gastrointestinal (GI) cancers such as gastro-esophageal cancer and hepatocellular carcinoma, with acceptable tolerability.[44] Pembrolizumab is a programmed death 1 monoclonal antibody (PD-1). It was approved for use in individuals who had previously been treated for advanced esophageal cancer and exhibited a median duration of response of 15 months in PD L1-positive gastroesophageal junction tumours.[45] Based on the results of the Check-Mate 040 trial, Nivolumab, another PD 1 inhibitor, received fast approval for patients with hepatocellular carcinoma. Patients with advanced hepatocellular carcinoma (HCC) who were intolerant to or unresponsive to sorafenib were given nivolumab and had a median survival of 15 months with a 15% response rate.[45]

In the Checkmate 459 clinical study, nivolumab is being tested as a first-line therapy for advanced HCC in

comparison to standard care with sorafenib (ClinicalTrials.gov identifier: NCT02576509). Pembrolizumab has also been approved as a second-line treatment for HCC patients who have failed to respond to or tolerate sorafenib. This approval was based on the KEYNOTE-224 trial, which was a single-arm, open-label study. There was a 17 percent overall response rate (ORR) [95 percent confidence interval (CI) 11–26], with a 1% complete response rate and a 16 percent partial response rate.[45] Immunotherapy, which is now being tested in a number of clinical trials across a variety of tumour types, has the potential to improve care for patients with GI-related diseases.

Immunotherapy's Future

Immune checkpoint inhibitors have demonstrated excellent tolerance, long-term effects, and even cure in some situations. The science of immunotherapy is rapidly expanding, with encouraging preliminary results. Immunotherapy has been studied not just as a monotherapy or in combination with various immune targeted treatments, but also in conjunction with radiation and conventional chemotherapy, as well as commencing immunotherapy at an earlier stage of malignancy in numerous current studies. Immune checkpoint drugs are being studied in MSS and MMR-p CRC in both adjuvant and metastatic situations in a number of active clinical trials.[46]

Vaccines for anti-tumor immunity

Another sort of immunotherapy is vaccine therapy. Vaccines are hypothesised to aid the anti-tumor response by inducing the immune system to target tumor-associated antigens. Autologous, peptide, and dendritic cell vaccines are among the vaccines tested in mCRC. When compared to normal therapy or placebo, cancer vaccinations have shown no effect in terms of survival.[47,48,49] Is there, however, a role for vaccinations in reawakening the immune system and transforming the tumour from immunological indolent to immune sensitive?Perhaps combining vaccinations with checkpoint inhibitors can provide a more immunogenic environment for the treatment of metastatic CRC? The results of the IMPALA phase III clinical study, which compared the TLR9 agonist Lefitolimod to standard of care as maintenance therapy in patients with mCRC, were disappointing. As a single-agent maintenance therapy, lefitolimod was not found to be superior.[49] Even though the results were unfavourable, they did not deter continued research into combination vaccine therapy.

Biomarkers of Immune Response

Microsatellite instability (MSI) has been identified as a biomarker for predicting the responsiveness to ICIs in solid malignancies. The KEYNOTE-016 study demonstrated MSI-H:efficacy dMMR's as a predictive biomarker for antiPD-1 therapy (pembrolizumab) in mCRC patients. In mCRC patients with MSI-H treated with PD-1 inhibitors, high DCR and favourable PFS were seen; however, less than half of the patients exhibited clinical response, implying that patients needed additional prognostic biomarkers. MSI-H tumours have a high tumour mutational burden (TMB), and studies have shown that TMB is typically elevated in MSI-H mCRC, although the reason for this is yet unknown.[50]

MSS has the best overall survival in mCRC patients treated with durvalumab and tremelimumab. Patients having a plasma TMB of 28 or more variations per megabase (HR, 0.34; 90 percent CI, 0.18-0.63; P =.004) had a lower risk of death.[51] TMB was strongly associated with objective response (OR; P0.001) and PFS by univariate (P0.001) and multivariate analysis (P0.01) in 22 patients treated with PD-1/L1 inhibitors, according to Schrock et al. TMB was strongly associated with objective response (OR; P0.001) and PFS by univariate (P0.001) and multivariate analysis (P0.01). Patients with high TMB did not reach the median PFS after an average follow-up of 18 months, but patients with low TMB had a median PFS of only 2 months. MSI-H mCRC is a modified version of the MSI-H mCRC.

Vaccine Therapy

Colorectal cancer overexpressed a number of tumor-associated antigens that could be used as a vaccine target in immunotherapy. Autologous, peptide, and dendritic cell vaccines are among the vaccines tested in mCRC In 10 mCRC patients, a phase I/II trial of the p53 synthetic long peptide (p53-SLP) vaccination was conducted. 67 percent of patients (six of nine) had p53-specific T-cell reactivity at six months, however polarised p53-specific CD4 + T cells accounted for only a minor proportion.

Future experiments should focus on how to increase the polarisation of the p53-SLP vaccine-induced T-cell response[52] In a phase 1/2 clinical trial using advanced-generation Ad5 [E1-, E2b-]-CEA(6D) vaccine in mCRC patients, Balint reported a decreased Treg to Teff cell ratio in samples from three of five patients and higher cytolytic T cell responses following immunizations. After a long period of observation, 20% of the patients were still alive, with a median survival time of 11 months.[53] In a phase I/II investigation, Morse et al. found that utilising VRP as vectors resulted in less neutralising antibodies and more CEA-specific T cell responses. Another study found that the 5-year RFS was 75%. No one died in people with stage III cancer (95 percent CI 40 to 91 percent). After immunisation, CD8+TEM rose and FOXP3 + Tregs decreased in 83 percent of patients (10/12). The findings suggested that VRP-CEA could help patients with stage III CRC live longer.[54, 55]

CHRONIC MYELOID LEUKEMIA

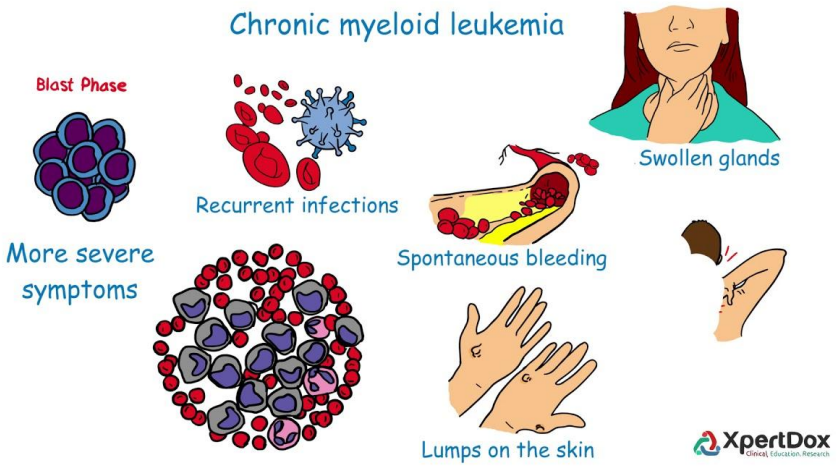


Figure 4.

Chronic myeloid leukaemia (CML) is a haematological malignancy marked by the presence of the BCR-ABL1 oncokinase, which is caused by a reciprocal translocation t(9;22) in the bone marrow's myeloid progenitor cells (BM). Tyrosine kinase inhibitors (TKIs), such as imatinib, nilotinib, dasatinib, and bosutinib, are currently the most commonly used therapy for CML.[56]

TKIs have dramatically improved the prognosis of chronic-phase CML patients, with treatment aimed at achieving a deep molecular response (DMR; MR4; BCR-ABL1mRNA 0.01%) and preventing disease progression. TKI withdrawal is possible in about half of patients who achieve DMR.[57] Leukemic stem cells (LSCs) that are dormant and self-renewing have been linked to refractoriness and disease development. These LSCs can persist even when there is no detectable residual disease, and can exit quiescence and cause relapse in response to changes in the BM microenvironment, posing a barrier to cure.

Immunologic surveillance of residual leukemic cells has recently been identified as a key role in maintaining treatment-free remission (TFR).[58,59,60,61] When the majority of CML cells have been eliminated below a particular threshold, immune cells are expected to be able to inhibit the proliferation of residual leukemic cells, resulting in long-term TFR. As a result, immunological characterisation and understanding of immune cell interactions with CML cells in the BM may aid in the development of novel immunotherapies that precisely target residual leukemic cells following TKI withdrawal to increase TFR rates.

Response to CML by the immune system

Prior to starting TKI medication, patients with CML have a period of immunological dysfunction. By preventing the host from developing antileukemia immunological responses, this aids tumour proliferation and self-preservation. In CML patients, innate immune responses such as dendritic cells (DCs)[62], plasmacytoid dendritic cells (pDCs), and natural killer (NK) cells (NK) cells[63] have been found to be dysfunctional, with losses in cell count, cytotoxicity, and antigen-presenting function.

Adaptive immunological responses, such as defective CD8+ cytotoxic T-cells (CTLs) and expressed/over-expressed leukemia-associated antigens (LAAs) such as proteinase-1 (PR1) and Wilm's tumor-1 (WT1), are dysfunctional in CML patients upon diagnosis.[64,65,66] CD8+ CTLs in CML-bearing mice similarly had low cytotoxic activity and did not produce interferon (IFN) or tumour necrosis factor (TNF).[66] Furthermore, CML CTLs contained high levels of programmed death 1 (PD1), which interacts with PD1 ligand (PDL1) produced on CML cells, causing cell killing to be suppressed and disease progression.[66] Immune suppressor cells, such as myeloid-derived suppressor cells (MDSCs) and regulatory T-cells (Tregs), play a role in T-cell dysfunction and disease progression in CML, with MDSCs and Tregs growing at diagnosis and decreasing after TKI therapy.[67,68,69]

After treatment with TKIs, the immune system responds in a positive way.

TKIs have a dual mode of action, inhibiting BCR-ABL1 tyrosine kinase directly while also having immune-modulatory or suppressive effects. The outcomes of in vitro and in vivo research have been shown to be contradictory. Imatinib and dasatinib have been shown to decrease immunological responses in several in vitro experiments. In vitro, both imatinib and dasatinib reversibly reduce T-cell proliferation, although dasatinib has a stronger effect.[70,71] Imatinib and dasatinib also block CD8+ CTLs that are selectively directed towards LAA in vitro.[72,73] and dasatinib also reduces NK cell activity.[73] In contrast to the in vitro findings, clinical data demonstrated that imatinib or dasatinib-treated

patients had an increase in CD8+ CTLs or NK cells, which is linked to a better therapeutic response.[74,75,76] Dasatinib may also cause reversible aberrant immunological reactivity, resulting in large granular lymphocytic lymphocytosis, which is linked to a beneficial clinical response. The inability to recapitulate all parts of the immune system and microenvironment is likely to be the cause of these disparities.

Imatinib-treated chronic-phase patients had a 20% chance of obtaining DMR in the first 2–3 years of therapy, with the second-generation TKIs dasatinib and nilotinib potentially allowing a faster DMR.[77,78] Immune-mediated management of residual illness is believed to govern the persistence of detectable leukemic cells when on or off treatment in DMR. In the peripheral blood of CML patients, DMR is linked to a rise in NK and CD8+ T-cell counts as well as a decrease in MDSCs. TFR success has also been linked to increased NK/CD8 T-cells, decreased Tregs/MDSCs, and low mature (CD86+) pDC frequency[79,80] Furthermore, combining IFN- with imatinib has been shown to improve results.[80,81] with multiple clinical studies demonstrating that IFN- in conjunction with TKI generates a long-lasting DMR, allowing TKI discontinuation.[84,85,86]

TKI in Combination Therapy for Chronic Phase CML

When interferon-alpha, daunorubicin, etoposide, and cytarabine (cytosine arabinoside, Ara-C) are combined with imatinib in vitro, preclinical studies suggest that they have an additive impact.[87,88] Interferon + TKI In patients with CML, interferon-alpha is successful as a monotherapy, and it was the treatment of choice prior to the introduction of imatinib.[89,90] Interferon-antileukemic alpha's effect is mediated by a direct anti-proliferative effect on CML progenitor cells,[91,92] but there may be another immunomodulatory mechanism at work.[93] The randomised IRIS study, which revealed considerable advantage of imatinib over interferon in combination with low-dose cytarabine, was the clinical trial that led to imatinib's registration.[94] Interferon monotherapy retained a limited role in clinical practise throughout the TKI era that followed, such as for patients who were TKI intolerant or couldn't take a TKI while pregnant.However, due to their distinct mechanisms of action, the possibility of combining TKI therapy with interferon therapy was quickly investigated. Early observations revealed dose-dependent toxicity, limiting the use of larger interferon cotreatment dosages.[95] Multiple studies found that combining interferon with imatinib at low doses was more practicable and resulted in higher rates of cytogenetic and molecular remission.Patients previously treated with interferon were shown to preserve their molecular remission numerically more commonly after imatinib termination in the STIM and A-STIM French TKI discontinuation studies, however without reaching statistical significance.[96,97] Patients who took interferon for a long time during their previous therapy (>1.5 years) had a higher likelihood of lasting TKI cessation, which was confirmed statistically significant in the big Euro-SKI trial that followed.[98] However, because the number of patients in this category was small, there was a possibility of selection bias.

Additional Routes

Much has been learned about the biology of CML and CML stem cells over the years, leading to the identification of numerous pathways that could be targeted. See Massimino et alstudy .'s for a very thorough review.[99] We'll go over a few of the most interesting investigations below.

Modulation of Immunity

Immune responses against CML-specific and CML-associated antigens such as BCR-ABL1, proteinase-3, and WT-1 can be found in CML patients[100], and donor lymphocyte infusions can cause long-lasting remissions in relapsed CML patients after treatment.[101] Several minor studies have looked into the possibility of eliciting an anti-leukemic immune response in CML patients. The use of ex vivo produced autologous dendritic cells as a vaccine is one option. After injection of ex-vivo produced autologous dendritic cells, this was found to induce a CML-specific T-cell response with proliferative capability. Another method is to vaccinate individuals with antigens linked to leukaemia. Injection of BCR-ABL derived peptides was found to be safe and effective, with the majority of patients experiencing a T-cell response. Some patients in these single-arm investigations demonstrated a decrease in cytogenetic and/or molecular depth.Treatment with immune checkpoint inhibitors could theoretically boost immune reactivity against leukemic cells in CML patients. Translational research indicates that activation of PD-L1 is an immune escape route for CML cells.[102] A phase 1 experiment utilising the PD-L1 inhibitor nivolumab in combination with dasatinib was recently completed with findings awaiting (ClinicalTrials.gov Identifier: NCT02011945), while the PD-L1 inhibitor avelumab is being investigated for CML patients in the ACTIW trial (ClinicalTrials.gov Identifier: NCT02767063).

Thiazolidinediones (PPAR-Agonists) are a type of thiazolidinedione.

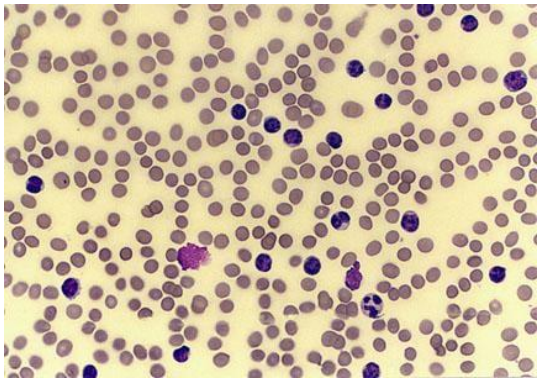
Thiazolidinediones are agonists of the peroxisome proliferator-activated receptor gamma (PPAR-) and are being studied as a synergistic co-treatment with TKI in CML. Thiazolidinediones, which serve as transcription factors to improve tissue sensitivity to insulin, are already utilised in clinical practise to treat diabetes. The PPAR-agonist pioglitazone encouraged CML cells to escape quiescence in vitro, making them more susceptible to imatinib's effects. STAT5 and its targets HIF2 and CITED2, which are overexpressed in CML stem cells, are downregulated by PPAR-agonists, which act as transcription factors .[103]

Gliptins are a kind of gliptin (DPPIV Inhibitors)

Gliptins, a medication class used to treat diabetes, are currently being studied for usage as a CML co-treatment. Dipeptidylpeptidase IV (DPPIV), also known as CD26, was shown to be overexpressed in Ph+CD34+ CML cells.[104] DPPIV is a membrane-bound cleaving protease that inactivates SDF1, leading in hematopoietic niche dysregulation. DPPIV isn't detectable in CD34+ hematopoietic cells from individuals with other myeloid neoplasms or healthy people.[104] DPPIV also inhibits the activity of other cytokines, such as incretins, which regulate insulin secretion after a meal. DPPIV inhibitors are used to treat diabetes because of this.The landscape of CML treatment has radically changed since the introduction of TKI therapy about 20 years ago, and the general prognosis of patients presenting in the chronic phase of the disease is excellent. TKI therapy, on the other hand, is not curative, and long-term use of TKIs is linked to chronic side effects, significant health risks, and a financial burden on health-care systems. Intolerance to TKIs is a common clinical issue. In addition, some patients acquire TKI resistance, which leads to progression to the advanced phase and, eventually, mortality from CML. Treatment-free remission is a new option for CML patients, although it is only possible for a limited percentage of them. Together,There are still a lot of unmet clinical needs, which emphasises the importance of continuing to look for new therapeutic options. Many options have been considered as our understanding of CML biology has grown. This could include using a new generation of targeted BCR-ABL1 inhibitors that target BCR-myristoyl ABL's pocket, as well as combining treatments with non-TKI medications like interferon or other drugs with unique targets relevant to CML biology.[104]

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukaemia (CLL) is a monoclonal disease defined by the buildup of functionally incompetent cells over time (see the histologic sample in the image below). Adults in Western countries are most commonly diagnosed with CLL, which is the most prevalent kind of leukaemia.[105] Because to CLL problems, some people die quickly, within 2-3 years after diagnosis, although the majority of patients live for 5-10 years.



Symptoms and signs

CLL patients experience a wide range of symptoms and indicators. CLL develops slowly, and it's not uncommon for it to be discovered by chance after a blood cell count is done for another reason; 25-50 percent of patients will be asymptomatic when they first appear.

The following are some of the signs and symptoms:

Lymphoma, liver, or spleen enlargement

Infections that recur

Appetite loss or early satiety

Bruising that is unusual (late-stage sign)

Fatigue

Sweats at night

Approach Points to Think About

Patients with chronic lymphocytic leukaemia (chronic lymphoid leukaemia, CLL) do not require treatment until they become symptomatic or show signs of rapid disease development, which includes the following:

Over the course of six months, I lost more than 10% of my body weight.

Extreme exhaustion

For more than two weeks, you've had a leukemia-related fever.

For more than a month, you've been sweating at night.

Marrow failure that gets worse with time (anemia or thrombocytopenia)

Anemia or thrombocytopenia caused by autoimmunity that does not respond to glucocorticoids

Splenomegaly can be progressive or symptomatic.

Lymphadenopathy that is either massive or symptomatic

Progressive lymphocytosis is defined as a 50% increase in 2 months or a doubling time of less than 6 months.

Patients with low-risk CLL who are stable merely need to be monitored on a regular basis. Early beginning of chemotherapy has been shown to have no benefit in CLL in many studies and a meta-analysis; in fact, it may increase mortality.[106,107] As a result, early therapy should only be explored as part of a clinical trial.

Efforts are being made to combine significant clinical, chromosomal, and serum indicators into a single nomogram/model. However, these tactics have failed to gain popular support.[108]

In CLL, a range of therapy regimens are used. Chemotherapy Regimens and Chronic Lymphocytic Leukemia Treatment Protocols are listed below. Nucleoside analogues, alkylating drugs, and biologics are frequently used in these regimens. The only known curative therapy is allogeneic stem cell transplantation. The absence of lymphocytosis, lymphadenopathy, and organomegaly without substantial cytopenias is considered a complete response (CR). CLL patients are susceptible to both common and uncommon infections. Vaccines against pneumococcal and influenza are advised. Growth factors may be administered to shorten the time that neutropenia lasts after chemotherapy.

It's worth noting that many CLL clinical trials involve a younger group that can handle strong treatment regimens and produce outstanding results. Various combination regimens have improved response rates but failed to show any survival benefit in multiple randomised trials.

The following are examples of common combination regimens:
FCR (fludarabine, cyclophosphamide, and rituximab) is a combination of fludarabine, cyclophosphamide, and rituximab.
Pentostatin, cyclophosphamide, and rituximab are three drugs used to treat cancer (PCR)
Fludarabine, cyclophosphamide, and mitoxantrone are all chemotherapy drugs (FCM)
Prednisone, vincristine, and cyclophosphamide (CVP)
Prednisone, cyclophosphamide, doxorubicin, vincristine, and doxorubicin (CHOP)
In previously untreated progressing CLL, Robak et colleagues found that cladribine or fludarabine in conjunction with cyclophosphamide is equally efficacious.[109] The authors found that cladribine or fludarabine plus cyclophosphamide are safe first-line regimens for progressive CLL; however, both combinations are ineffective in patients with 17p13 (TP53 gene) deletion. The combination of bendamustine and rituximab has reawakened attention. The total response rate was 59 percent in a German phase II study of 72 pretreated patients, and progression-free survival (PFS) was nearly 15 months.[110]

Targeted therapy in various combinations are the current emphasis in CLL. Chemoimmunotherapy has already been shown to be inferior to these. Chemoimmunotherapy is currently reserved for young, fit patients with good CLL characteristics, who make up less than 10% of all CLL cases. Even such patients may prefer targeted therapy due to the possibility of subsequent malignancies (e.g., myelodysplastic syndromes, acute myeloid leukaemia).[111]

Bendamustine
A phase III trial comparing bendamustine to chlorambucil in treatment-naive patients who were not candidates for more aggressive regimens like FCR found no difference in overall survival, but complete response was higher (21 percent vs 10 percent) and PFS was longer with bendamustine than with c hlorambucil (21 months vs 9 months). Bendamustine did not have any negative effects on quality of life.[112]

Alemtuzumab
Alemtuzumab is a CD52-targeting monoclonal antibody that has been licenced for use in CLL as a first-line treatment and as a salvage treatment in patients with fludarabine-resistant illness. Alemtuzumab has been found to help those with CLL who had p53 mutations. This is in contrast to rituximab, which is ineffective in CLL patients with a p53 mutation. Alemtuzumab has showed only modest effectiveness in clearing bulky lymphadenopathy, despite being quite effective in clearing illness from the bone marrow.

Alemtuzumab appears to play a role in the eradication of minimal residual disease after consolidation therapy.[113,114] In one research, alemtuzumab consolidation after induction chemotherapy resulted in molecular disease remission in 38% of patients. Three patients in this study developed Epstein-Barr virus–positive large B-cell lymphoma, two of which cleared spontaneously and the third of which responded to cidofovir and immunoglobulin. Two phase II studies looked at aggressive CFAR (FCR and alemtuzumab) treatment as a frontline[115] and salvage treatment for high-risk CLL.[116] In the frontline study, the median PFS was 38 months, however the median overall survival was not met.

In selected patients with excellent performance status, the therapy may be of relevance as a regimen to achieve complete response in the 17p deletion CLL population before allogeneic stem cell transplantation. The addition of alemtuzumab to FCR did not increase PFS or overall survival in pretreated patients when administered as salvage when compared to FCR. In 74 percent of patients, serious infections developed during or after therapy.[116] Due to significant infections in the alemtuzumab arm, the German CLL Study Group prematurely halted a phase III trial utilising alemtuzumab consolidation; however, this has not been encountered in other studies to date.

For patients taking alemtuzumab during and for 2-4 months following therapy, or until their CD4 count surpasses 250 109 cells, antiviral prophylaxis and prophylactic medications for Pneumocystis jiroveci are indicated. The polymerase chain reaction (PCR) for cytomegalovirus (CMV) is also advised for monitoring CMV reactivation. If CMV is found, alemtuzumab should be stopped and proper therapy started until the virus is no longer detectable.

When alemtuzumab was compared to rituximab, a 2012 Cochrane Database review of five randomised controlled trials (845 participants) found no increase in survival or PFS (2 trials). When alemtuzumab was compared to chlorambucil, PFS (but not overall survival) was enhanced, but at the cost of higher CMV infections in the alemtuzumab arm (1 trial). Alemtuzumab was superior to no therapy for overall survival in one of the two trials analysed, although one of the two trials had to be prematurely closed due to serious infections in the alemtuzumab group. As a result, we continue to prescribe alemtuzumab exclusively for patients who have a p53 mutation (p17) and who have failed to respond to a fludarabine-based treatment Because of its toxicity, it has failed as a first-line treatment.[117]
Monoclonal antibodies are antibodies that are produced in a single cell.
The following is a list of resources. Monoclonal antibodies have been approved for use in the treatment of CLL.
Ofatumumab
Obinutuzumab \ Duvelisib
hLL1, epratuzumab, and lumiliximab are three more monoclonal antibodies under development for CLL

research. Despite promising results in a phase I/II trial, a phase III trial comparing FCR with and without lumiliximab in patients with recurrent CLL was halted early after an interim analysis revealed that the combination of lumiliximab and FCR did not provide sufficient effectiveness.[118]

Ofatumumab

The US Food and Drug Administration (FDA) approved ofatumumab (Arzerra), an anti-CD20 monoclonal antibody, in 2010 for CLL that is resistant to fludarabine and alemtuzumab.[119] Ofatumumab is also licenced for use with chlorambucil in untreated patients with CLL who do not respond to fludarabine-based therapy.[120] The FDA granted approval based on the findings of a multicenter, randomised, open-label trial including 447 patients who were not candidates for fludarabine-based therapy. The combined ofatumumab and chlorambucil treatment resulted in a median PFS of 22.4 months compared to 13.1 months with chlorambucil monotherapy (P 0.001).[121] The indication for ofatumumab was increased in January 2016 to cover extended treatment as a single agent for patients with recurrent or progressive CLL who have achieved a complete or partial response after at least two lines of therapy.[122] The indication for ofatumumab was expanded in August 2016 to include usage in relapsed CLL in combination with fludarabine and cyclophosphamide. The COMPLEMENT 2 international study (N = 365) in patients with relapsed CLL was used to gain approval. PFS was 28.9 months with ofatumumab plus fludarabine and cyclophosphamide (OFC) versus 18.8 months with fludarabine and cyclophosphamide alone (FC) (P=0.0032). The addition of ofatumumab was well tolerated, according to reports. Overall survival in the OFC arm was 56.4 months compared to 45.8 months in the FC arm (P=0.1410).[123]

Obinutuzumab

Another CD20-directed cytolytic monoclonal antibody is obinutuzumab (Gazyva). In 2013, the FDA authorised it in combination with chlorambucil for previously untreated CLL. Obinutuzumab is the first medicine to be approved by the FDA as a breakthrough therapy. Obintuzumab has been given this classification because it has the potential to provide a significant improvement over current therapy for patients with serious or life-threatening disorders. The FDA approved obinutuzumab after a pivotal phase III trial in 356 previously untreated CLL patients (mean age, 73 years), which found that median PFS was significantly better in patients who received obinutuzumab in combination with chlorambucil than in patients who received chlorambucil alone (23 vs 11.1 mo; P 0.0001).[124] The use of chlorambucil as a monotherapy was effectively discontinued as a result of these findings.[125]

Duvelisib

Duvelisib (Copiktra) was approved in 2018 for individuals with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) who had previously had at least two treatments. Duvelisib reduced the risk of disease progression or mortality by 48 percent compared to ofatumumab in the phase III DUO clinical trial (n=319), and more patients responded to duvelisib than to ofatumumab (73.8 percent vs 45.3 percent; P 0.0001 for both CLL and SLL). Patients treated with duvelisib had a longer median PFS (13.3 vs 9.9 months; p 0.0001), including those with the del(17p) mutation (12.7 vs 9.0 months; P = 0.0011). The two treatment cohorts (P = 0.48).[126]

Monoclonal antibodies in combination therapy

Monoclonal antibodies have been used with chemotherapeutic drugs in clinical trials. Rituximab has only had partial, short-term responses when administered alone, although it has been used frequently in combination with chemotherapeutic medicines (eg, fludarabine). Patients with trisomy 12q may have greater levels of CD20, making tumour cells more susceptible to CD20-targeting biologics.[127]

Fludarabine has been demonstrated to reduce the expression of CD55 and CD59, which are proteins implicated in complement resistance, and their absence improves the effectiveness of rituximab. In clinical trials, fludarabine with rituximab resulted in better clinical remission rates than fludarabine alone. The median overall survival was 85 months in a prospective, single-arm study of individuals treated first with fludarabine and rituximab.[128] Seventy-one percent of patients were alive after five years, and twenty-seven percent were disease-free. In salvage therapy for individuals with previously treated CLL, the combination of fludarabine and cyclophosphamide with rituximab (FCR) has demonstrated to yield superior clinical response rates than either fludarabine or fludarabine plus cyclophosphamide (FC). In a trial of 552 individuals with previously treated CLL, Robak et al observed that median PFS was 30.6 months with FCR versus 20.6 months with FC following a median follow-up of 25 months. Patients who had FCR also had a superior event-free survival rate, response rate, complete response rate, duration of response, and time to new CLL treatment or death.[129]

PFS was 65 percent with FCR versus 45 percent with FC three years after randomization in treatment-naive individuals with CD20-positive CLL. Overall survival was 87 percent in one group and 83 percent in the other. Neutropenia and leukocytopenia of grade 3 and 4 were more common with FCR, although other side effects, such as severe infections, were not.[130]

Fludarabine plus alemtuzumab (n=168) resulted in a longer PFS than fludarabine alone (n=167; median 23.7 months versus 16.5 months, P=00003) in patients with previously treated CLL, according to a phase III research. The combination also resulted in a higher overall survival rate.[131] Cyclophosphamide, fludarabine,

alemtuzumab, and rituximab are used in conjunction to treat cancer. In a study of 781 treatment-naive CLL patients, the combination of obinutuzumab/chlorambucil was found to be superior than rituximab/chlorambucil.[132] The obinutuzumab/chlorambucil group had a median PFS of 27 months, compared to 15 months in the rituximab/chlorambucil group; the overall response rate was 78 percent versus 65 percent, respectively. Minimum residual disease (MRD) in bone marrow was 19.5 percent in obinutuzumab/chlorambucil patients, compared 2.6 percent in rituximab/chlorambucil patients, while MRD in blood was 37.7% and 3.3 percent, respectively, at the conclusion of treatment.[132]

Combinations of targeted therapies

The combination of venetoclax and obinutuzumab was authorised by the FDA in 2019 for use in individuals with previously untreated CLL.[133] Standard regimens, on the other hand, must be continued for extended periods of time, or even permanently, whereas the combination must be taken for only one year. After 12 cycles, 88 percent of patients in a phase II study of the combination of ibrutinib and venetoclax in 80 previously untreated high-risk and older patients with CLL had complete remission or complete remission with incomplete count recovery, and 61 percent of patients had remission with undetectable MRD.[133] However, because this combination has not yet been approved for clinical use, it should be used with caution. Treatment with venetoclax plus rituximab resulted in an 84.9 percent 2-year rate of progression-free survival in 389 patients with relapsed or refractory CLL, compared to 36.3 percent in patients treated with bendamustine plus rituximab (hazard ratio for progression or death, 0.17; 95 percent confidence interval [CI], 0.11 to 0.25; P 0.001). All clinical and biologic categories, including patients with and without chromosome 17p deletion, saw a benefit from venetoclax-rituximab.[134] PFS and overall survival remained higher with venetoclax-rituximab during a median follow-up of 36 months in a post-therapy study, confirming the practicality of the treatment.

Table. International Prognostic Score for Early-stage CLL

Score	Risk Category	5-year cumulative risk for treatment start
0	Low	8.4%
1	Intermediate	28.4%
2-3	High	61.2%

CONCLUSION

In conclusion, with the advent of cancer immunotherapy and recent advances in the field, cancer patients appear to have a real chance of being cured. Cancer treatment has been changed by the development of cancer vaccines, CAR-T cells, and checkpoint inhibitors. Combination therapy could be a promising cancer treatment technique in the future. The ability to recognise and control the side effects of cancer immunotherapy will also be critical to treatment effectiveness. The most promising cancer therapy tactics will be personalised combination treatments that use new techniques to target each patient's disease biology.

ACKNOWLEDGEMENT

I would like to express my special thanks and gratitude to my guide DR.HAJEERA FATHIMA mam for giving me the topic and encouraged to in writing this review.

NO CONFLICT OF INTRESTS

REFERENCES

1. Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH Jr. A review of cancer immunotherapy: from the past, to the present, to the future. *Curr Oncol*, 2020; 27(Suppl 2): S87-S97. doi:10.3747/co.27.5223.
2. Oiseth SJ, Aziz MS. Cancer immunotherapy: a brief review of the history, possibilities, and challenges ahead. *J Cancer Metastasis Treat*, 2017; 3: 250-261. http://dx.doi.org/10.20517/2394-4722.2017.41.
3. Guobing Chen, Monica Bodogai, ATamehiro, Chuanlai Shen, Jun Dou, "Cancer Immunotherapy: Theory and Application", Journal of Immunology Research, vol. 2018, Article ID 7502161, 2 pages, 2018. https://doi.org/10.1155/2018/7502161
4. Waldman, A.D., Fritz, J.M. & Lenardo, M.J. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol*, 2020; 20: 651–668. https://doi.org/10.1038/s41577-020-0306-5
5. Lucy Boyce Kennedy MD,April K. S. Salama MD, A review of cancer immunotherapy toxicity published: 16 January 2020. https://doi.org/10.3322/caac.21596
6. Ishida, Y., Agata, Y., Shibahara, K. & Honjo, T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J*, 1992; 11: 3887–3895. Using subtractive hybridization, this study is the first to identify PD1 as a new immunoglobulin superfamily member expressed within the thymus.
7. Carreno, B. M. & Collins, M. The B7 family of ligands and its receptors: new pathways for costimulation and inhibition of immune responses. *Annu. Rev. Immunol*, 2002; 20: 29–53.
8. Latchman, Y. et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat. Immunol*, 2001; 2: 261–268.
9. Francisco, L. M., Sage, P. T. & Sharpe, A. H. The PD-1 pathway in tolerance and autoimmunity. *Immunol. Rev*, 2010; 236: 219–242.
10. Freeman, G. J. et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J. Exp. Med*, 2000; 192: 1027–1034. This study demonstrates that a new B7 family member,

PDL1, functions as a ligand for PD1 in order to dampen T cell activation.
11. Nishimura, H., Minato, N., Nakano, T. & Honjo, T. Immunological studies on PD-1 deficient mice: implication of PD-1 as a negative regulator for B cell responses. *Int. Immunol*, 1998; 10: 1563–1572.
12. Nishimura, H., Nose, M., Hiai, H., Minato, N. & Honjo, T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*, 1999; 11: 141–151.
13. Iwai, Y. et al. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc. Natl Acad. Sci. USA*, 2002; 99: 12293–12297. This study shows that PDL1 expression by tumour cells represents a mechanism of resistance to immune-mediated cytolysis that can be abrogated by blockade of the PD1 axis.
14. Hirano, F. et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*, 2005; 65: 1089–1096. This preclinical murine study shows that blockade of PD1 or PDL1 could reverse inherent resistance of tumours to cytolysis by T cells.
15. Strome, S. E. et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res*, 2003; 63: 6501–6505.
16. Iwai, Y., Terawaki, S. & Honjo, T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int. Immunol*, 2005; 17: 133–144. Beyond enhancing antitumoural immunity, this study demonstrates that PD1 blockade can limit tumour metastatic potential.
17. Hamanishi, J. et al. Programmed cell death 1 ligand 1 and tumor-infiltrating $CD8^+$ T lymphocytes are prognostic factors of human ovarian cancer. *Proc. Natl Acad. Sci. USA*, 2007; 104: 3360–3365.
18. Thompson, R. H. et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin. Cancer Res*, 2021; 13: 1757–1761.
19. Thompson, R. H. et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res*, 2006; 66: 3381–3385. Along with Thompson et al. (2020) and Hamanishi et al. (2020), this study shows that expression of PD1 on tumour-infiltrating T cells and PD1 ligands on tumours are poor prognostic markers in various cancers.
20. Southam, C. M., Brunschwig, A., Levin, A. G. & Dizon, Q. S. Effect of leukocytes on transplantability of human cancer. *Cancer*, 1966; 19: 1743–1753. This clinical study is the first to demonstrate the viability of using patient-derived leukocytes and autologous tumour cells to promote cancer regression.
21. Rosenberg, S. A. et al. Use of tumor-infiltrating lymphocytes and interleukin-2 in the immunotherapy of patients with metastatic melanoma. A preliminary report. *N. Engl. J. Med*, 1988; 319: 1676–1680.
22. Rosenberg, S. A. et al. Treatment of patients with metastatic melanoma with autologous tumor-infiltrating lymphocytes and interleukin 2. *J. Natl Cancer Inst*, 1994; 86: 1159–1166.
23. Weiden, P. L. et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *N. Engl. J. Med*, 1979; 300: 1068–1073.
24. Rosenberg, S. A. et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin. Cancer Res*, 2011; 17: 4550–4557. This study expands on the clinical success of IL-2-expanded tumour-infiltrating lymphocytes in cancer treatment through the addition of lymphodepletion before administration of the cellular therapy.
25. Zacharakis, N. et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. *Nat. Med*, 2018; 24: 724–730.
26. Palmer, D. C. et al. Cish actively silences TCR signaling in $CD8^+$ T cells to maintain tumor tolerance. *J. Exp. Med*, 2015; 212: 2095.
27. Perica, K., Varela, J. C., Oelke, M. & Schneck, J. Adoptive T cell immunotherapy for cancer. *Rambam Maimonides Med. J*, 2015; 6: e0004.
28. Brudno, J. N. & Kochenderfer, J. N. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*, 2016; 127: 3321–3330. This review details the adverse effects associated with CAR T cell therapy and their subsequent clinical management.
29. Neelapu, S. S. et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. *Nat. Rev. Clin. Oncol*, 2018; 15: 47–62.
30. Giavridis, T. et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. *Nat. Med*, 2018; 24: 731–738.
31. Ghorashian, S. et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat. Med*, 2019; 25: 1408–1414.
32. Bielamowicz, K. et al. Trivalent CAR T cells overcome interpatient antigenic variability in glioblastoma. *Neuro Oncol*, 2018; 20: 506–518.
33. Hung, C. F. et al. Development of anti-human mesothelin-targeted chimeric antigen receptor messenger RNA-transfected peripheral blood lymphocytes for ovarian cancer therapy. *Hum. Gene Ther*, 2018; 29: 614–625.
34. Jones, B. S., Lamb, L. S., Goldman, F. & Di Stasi, A. Improving the safety of cell therapy products by suicide gene transfer. *Front. Pharmacol*, 2014; 5: 254–254.

35. Hernandez, I., Prasad, V. & Gellad, W. F. Total costs of chimeric antigen receptor T-cell immunotherapy. *JAMA Oncol,* 2018; 4: 994–996.
36. Moon, E. K., Langer, C. J. & Albelda, S. M. The era of checkpoint blockade in lung cancer: taking the brakes off the immune system. *Ann. Am. Thorac. Soc*, 2017; 14: 1248–1260.
37. Vormittag, P., Gunn, R., Ghorashian, S. & Veraitch, F. S. A guide to manufacturing CAR T cell therapies. *Curr. Opin. Biotechnol*, 2018; 53: 164–181.
38. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin,* 2019; 69: 7–34. [PubMed] [Google Scholar]
39. Cronin KA, Lake AJ, Scott S, et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. *Cancer,* 2018; 124: 2785–2800. [PMC free article] [PubMed] [Google Scholar]
40. Goodwin RA, Asmis TR. Overview of systemic therapy for colorectal cancer. *Clin Colon Rectal Surg*, 2009; 22: 251–256. [PMC free article] [PubMed] [Google Scholar]
41. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med,* 2000; 343: 905–914. [PubMed] [Google Scholar]
42. Stein A, Moehler M, Trojan J, et al. Immuno-oncology in GI tumours: clinical evidence and emerging trials of PD-1/PD-L1 antagonists. *Crit Rev Oncol Hematol*, 2018; 130: 13–26. [PubMed] [Google Scholar]
43. Grierson P, Lim KH, Amin M. Immunotherapy in gastrointestinal cancers. *J Gastrointest Oncol*, 2017; 8: 474–484. [PMC free article] [PubMed] [Google Scholar]
44. Doi T, Piha-Paul SA, Jalal SI, et al. Safety and antitumor activity of the anti-programmed death-1 antibody Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol,* 2018; 19: 940–952. [PubMed] [Google Scholar]pembrolizumab in patients with advanced esophageal carcinoma. *J Clin Oncol,* 2018; 36: 61–67. [PubMed] [Google Scholar]
45. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*, 2017; 389: 2492–2502. [PMC free article] [PubMed] [Google Scholar]
46. Schulze T, Kemmner W, Weitz J, et al. Efficiency of adjuvant active specific immunization with Newcastle disease virus modified tumor cells in colorectal cancer patients following resection of liver metastases: results of a prospective randomized trial. *Cancer Immunol Immunother*, 2009; 58: 61–69. [PubMed] [Google Scholar]
47. Hazama S, Nakamura Y, Tanaka H, et al. A phase II study of five peptides combination with oxaliplatin-based chemotherapy as a first-line therapy for advanced colorectal cancer (FXV study). *J Transl Med,* 2014; 12: 108. [PMC free article] [PubMed] [Google Scholar]
48. Lazoura E, Apostolopoulos V. Rational peptide-based vaccine design for cancer immunotherapeutic applications. *Curr Med Chem*, 2005; 12: 629–639. [PubMed] [Google Scholar]
49. Okuno K, Sugiura F, Inoue K, et al. Clinical trial of a 7-peptide cocktail vaccine with oral chemotherapy for patients with metastatic colorectal cancer. *Anticancer Res,* 2014; 34: 3045–3052. [PubMed] [Google Scholar]
50. Newman J, Seetharamu N, Saif MW. Burden of Proof: Evaluating the Efficacy of Tumor Mutational Burden (TMB) in Predicting Response to Immune Checkpoint Inhibitors. *Cancer Med J,* 2020; 3(Suppl 2): 17–21. PubMed Abstract | Google Scholar
51. Chen EX, Jonker DJ, Loree JM, Kennecke HF, Berry SR, Couture F, et al. Effect of Combined Immune Checkpoint Inhibition vs Best Supportive Care Alone in Patients With Advanced Colorectal Cancer: The Canadian Cancer Trials Group CO.26 Study. *JAMA Oncol,* 2020; 6(6): 831–8. doi: 10.1001/jamaoncol.2020.0910PubMed Abstract | CrossRef Full Text | Google Scholar
52. Speetjens FM, Kuppen PJ, Welters MJ, Essahsah F, Voet van den Brink AM, Lantrua MG, et al. Induction of p53-Specific Immunity by a p53 Synthetic Long Peptide Vaccine in Patients Treated for Metastatic Colorectal Cancer. *Clin Cancer Res an Off J Am Assoc Cancer Res*, 2009; 15(3): 1086–95. doi: 10.1158/1078-0432.ccr-08-2227. CrossRef Full Text | Google Scholar
53. Balint JP, Gabitzsch ES, Rice A, Latchman Y, Xu Y, Messerschmidt GL, et al. Extended Evaluation of a Phase 1/2 Trial on Dosing, Safety, Immunogenicity, and Overall Survival After Immunizations With an Advanced-Generation Ad5 [E1-, E2b-]-CEA(6D) Vaccine in Late-Stage Colorectal Cancer. *Cancer Immunol Immunother CII,* 2015; 64(8): 977–87. doi: 10.1007/s00262-015-1706-4. CrossRef Full Text | Google Scholar
54. Morse MA, Hobeika AC, Osada T, Berglund P, Hubby B, Negri S, et al. An Alphavirus Vector Overcomes the Presence of Neutralizing Antibodies and Elevated Numbers of Tregs to Induce Immune Responses in Humans With Advanced Cancer. *J Clin Invest,* 2010; 120(9): 3234–41. doi: 10.1172/jci42672PubMed Abstract | CrossRef Full Text | Google Scholar
55. Crosby EJ, Hobeika AC, Niedzwiecki D, Rushing C, Hsu D, Berglund P, et al. Long-Term Survival of Patients With Stage III Colon Cancer Treated With VRP-CEA(6D), an Alphavirus Vector That Increases the CD8+ Effector Memory T Cell to Treg Ratio. *J Immunother Cancer,* 2020; 8(2): e001662.

doi: 10.1136/jitc-2020-00166 PubMed Abstract | CrossRef Full Text | Google Scholar
56. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia, 2020; 34: 966–84.
57. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol, 2018; 19: 747–57.
58. Ilander M, Olsson-Stromberg U, Schlums H, Guilhot J, Bruck O, Lahteenmaki H, et al. Increased proportion of mature NK cells is associated with successful imatinib discontinuation in chronic myeloid leukemia. Leukemia, 2017; 31: 1108–16.
59. Schutz C, Inselmann S, Saussele S, Dietz CT, Mu Ller MC, Eigendorff E, et al. Expression of the CTLA-4 ligand CD86 on plasmacytoid dendritic cells (pDC) predicts risk of disease recurrence after treatment discontinuation in CML. Leukemia, 2017; 31: 829–36.
60. Rea D, Henry G, Khaznadar Z, Etienne G, Guilhot F, Nicolini F, et al. Natural killer-cell counts are associated with molecular relapse-free survival after imatinib discontinuation in chronic myeloid leukemia: the IMMUNOSTIM study. Haematologica, 2017; 102: 1368–77.
61. Caocci G, Martino B, Greco M, Abruzzese E, Trawinska MM, Lai S, et al. Killer immunoglobulin-like receptors can predict TKI treatment-free remission in chronic myeloid leukemia patients. Exp Hematol, 2015; 43: 1015–8.e1011.
62. Dong R, Cwynarski K, Entwistle A, Marelli-Berg F, Dazzi F, Simpson E, et al. Dendritic cells from CML patients have altered actin organization, reduced antigen processing, and impaired migration. Blood, 2003; 101: 3560–7.
63. Nakajima H, Zhao R, Lund TC, Ward J, Dolan M, Hirsch B, et al. The BCR/ABL transgene causes abnormal NK cell differentiation and can be found in circulating NK cells of advanced phase chronic myelogenous leukemia patients. J Immunol, 2002; 168: 643–50.
64. Bruck O, Blom S, Dufva O, Turkki R, Chheda H, Ribeiro A, et al. Immune cell contexture in the bone marrow tumor microenvironment impacts therapy response in CML. Leukemia, 2018; 32: 1643–56.
65. Molldrem JJ, Lee PP, Wang C, Felio K, Kantarjian HM, Champlin RE, et al. Evidence that specific T lymphocytes may participate in the elimination of chronic myelogenous leukemia. Nat Med, 2000; 6: 1018–23.
66. Mumprecht S, Schurch C, Schwaller J, Solenthaler M, Ochsenbein AF. Programmed death 1 signaling on chronic myeloid leukemia-specific T cells results in T-cell exhaustion and disease progression. Blood, 2009; 114: 1528–36.
67. Giallongo C, Parrinello N, Tibullo D, La Cava P, Romano A, Chiarenza A, et al. Myeloid derived suppressor cells (MDSCs) are increased and exert immunosuppressive activity together with polymorphonuclear leukocytes (PMNs) in chronic myeloid leukemia patients. PLoS ONE, 2014; 9: e101848.
68. Hughes A, Clarson J, Tang C, Vidovic L, White DL, Hughes TP, et al. CML patients with deep molecular responses to TKI have restored immune effectors and decreased PD-1 and immune suppressors. Blood, 2017; 129: 1166–76.
69. Najima Y, Yoshida C, Iriyama N, Fujisawa S, Wakita H, Chiba S, et al. Regulatory T cell inhibition by dasatinib is associated with natural killer cell differentiation and a favorable molecular response—The final results of the D-first study. Leuk Res, 2018; 66: 66–72.
70. Seggewiss R, Lore K, Greiner E, Magnusson MK, Price DA, Douek DC, et al. Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. Blood, 2005; 105: 2473–9.
71. Schade AE, Schieven GL, Townsend R, Jankowska AM, Susulic V, Zhang R, et al. Dasatinib, a small-molecule protein tyrosine kinase inhibitor, inhibits T-cell activation and proliferation. Blood, 2008; 111: 1366–77.
72. Chen J, Schmitt A, Chen B, Rojewski M, Ringhoffer M, von Harsdorf S, et al. Imatinib impairs CD8+ T lymphocytes specifically directed against the leukemia-associated antigen RHAMM/CD168 in vitro. Cancer Immunol Immunother, 2007; 56: 849–61.
73. Weichsel R, Dix C, Wooldridge L, Clement M, Fenton-May A, Sewell AK, et al. Profound inhibition of antigen-specific T-cell effector functions by dasatinib. Clin Cancer Res, 2008; 14: 2484–91.
74. Blake SJ, Bruce Lyons A, Fraser CK, Hayball JD, Hughes TP. Dasatinib suppresses in vitro natural killer cell cytotoxicity. Blood, 2008; 111: 4415–6.
75. Mustjoki S, Ekblom M, Arstila TP, Dybedal I, Epling-Burnette PK, Guilhot F, et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. Leukemia, 2009; 23: 1398–405.
76. Chang MC, Cheng HI, Hsu K, Hsu YN, Kao CW, Chang YF, et al. NKG2A down-regulation by dasatinib enhances natural killer cytotoxicity and accelerates effective treatment responses in patients with chronic myeloid leukemia. Front Immunol, 2018; 9: 3152.
77. Kreutzman A, Yadav B, Brummendorf TH, Gjertsen BT, Hee Lee M, Janssen J, et al. Immunological monitoring of newly diagnosed CML patients treated with bosutinib or imatinib first-line. Oncoimmunology, 2019; 8: e1638210.
78. Hughes TP, Saglio G, Kantarjian HM, Guilhot F, Niederwieser D, Rosti G, et al. Early molecular

response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood, 2014; 123: 1353–60.
79. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boque C, et al. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol, 2016; 34: 2333–40.
80. Irani YD, Hughes A, Clarson J, Kok CH, Shanmuganathan N, White DL, et al. Successful treatment-free remission in chronic myeloid leukaemia and its association with reduced immune suppressors and increased natural killer cells. Br J Haematol, 2020; 191: 433–41.
81. Cayssials E, Jacomet F, Piccirilli N, Lefevre L, Roy L, Guilhot F, et al. Sustained treatment-free remission in chronic myeloid leukaemia is associated with an increased frequency of innate CD8(+) T-cells. Br J Haematol, 2019; 186: 54–59.
82. Nicolini FE, Hayette S, Legros L, Rousselot P, Maloisel F, Tulliez M, et al. Pegylated IFN-alpha2a combined to imatinib mesylate 600mg daily can induce complete cytogenetic and molecular responses in a subset of chronic phase CML patients refractory to IFN alone or to imatinib 600mg daily alone. Leuk Res, 2011; 35: 80–86.
83. Palandri F, Castagnetti F, Iacobucci I, Martinelli G, Amabile M, Gugliotta G, et al. The response to imatinib and interferon-alpha is more rapid than the response to imatinib alone: a retrospective analysis of 495 Philadelphia-positive chronic myeloid leukemia patients in early chronic phase. Haematologica, 2010; 95: 1415–9.
84. Burchert A, Muller MC, Kostrewa P, Erben P, Bostel T, Liebler S, et al. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. J Clin Oncol, 2010; 28: 1429–35.
85. Hjorth-Hansen H, Stentoft J, Richter J, Koskenvesa P, Hoglund M, Dreimane A, et al. Safety and efficacy of the combination of pegylated interferon-alpha2b and dasatinib in newly diagnosed chronic-phase chronic myeloid leukemia patients. Leukemia, 2016; 30: 1853–60.
86. Burchert A, Saussele S, Eigendorff E, Muller MC, Sohlbach K, Inselmann S, et al. Interferon alpha 2 maintenance therapy may enable high rates of treatment discontinuation in chronic myeloid leukemia. Leukemia, 2015; 29: 1331–5.
87. Thiesing JT, Ohno-Jones S, Kolibaba KS, Druker BJ. Efficacy of STI571, an abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against bcr-abl-positive cells. *Blood*, 2000; 96: 3195–9. Available online at: http://www.bloodjournal.org/content/96/9/3195PubMed Abstract | Google Scholar
88. Topaly J, Zeller WJ, Fruehauf S. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor STI571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. *Leukemia*, 2001; 15: 342–7. doi: 10.1038/sj.leu.2402041PubMed Abstract | CrossRef Full Text | Google Scholar
89. Talpaz M, Kantarjian H, Kurzrock R, Trujillo JM, Gutterman JU. Interferon-alpha produces sustained cytogenetic responses in chronic myelogenous leukemia. Philadelphia chromosome-positive patients. *Ann Intern Med*, 1991; 114: 532–8.PubMed Abstract | Google Scholar
90. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-alpha therapy. The Leukemia Service. *Ann Intern Med*, 1995; 122: 254–61.PubMed Abstract | Google Scholar.
91. Cornelissen JJ, Ploemacher RE, Wognum BW, Borsboom A, Kluin-Nelemans HC, Hagemeijer A, et al. An *in vitro* model for cytogenetic conversion in CML. Interferon-alpha preferentially inhibits the outgrowth of malignant stem cells preserved in long-term culture. *J Clin Invest*, 1998; 102: 976–83. doi: 10.1172/JCI2366PubMed Abstract | CrossRef Full Text | Google Scholar.
92. Gordon MY, Marley SB, Lewis JL, Davidson RJ, Nguyen DX, Grand FH, et al. Treatment with interferon-alpha preferentially reduces the capacity for amplification of granulocyte-macrophage progenitors (CFU-GM) from patients with chronic myeloid leukemia but spares normal CFU-GM. *J Clin Invest*, 1998; 102: 710–5. doi: 10.1172/JCI3094PubMed Abstract | CrossRef Full Text | Google Scholar.
93. Guilhot F, Roy L, Guilhot J, Millot F. Interferon therapy in chronic myelogenous leukemia. *Hematol Oncol Clin North Am*, 2004; 18: 585–603, viii. doi: 10.1016/j.hoc.2004.03.002PubMed
Abstract | CrossRef Full Text | Google Scholar.
94. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*, 2003; 348: 994–1004. doi: 10.1056/NEJMoa022457PubMed
Abstract | CrossRef Full Text | Google Scholar
95. Baccarani M, Martinelli G, Rosti G, Trabacchi E, Testoni N, Bassi S, et al. Imatinib and pegylated human recombinant interferon-alpha2b in early chronic-phase chronic myeloid leukemia. *Blood*, 2004; 104: 4245–51. doi: 10.1182/blood-2004-03-0826PubMed Abstract | CrossRef Full Text | Google Scholar
96. Mahon FX, Rea D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*, 2010; 11: 1029–35. doi: 10.1016/S1470-2045(10)70233.

97. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*, 2014; 32: 424–30. doi: 10.1200/JCO.2012.48.5797.
98. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*, 2018; 19: 747–57.
99. Massimino M, Stella S, Tirro E, Romano C, Pennisi MS, Puma A, et al. Non ABL-directed inhibitors as alternative treatment strategies for chronic myeloid leukemia. *Mol Cancer*, 2018; 17: 56. doi: 10.1186/s12943-018-0805-1.
100. Brauer KM, Werth D, von Schwarzenberg K, Bringmann A, Kanz L, Grunebach F, et al. BCR-ABL activity is critical for the immunogenicity of chronic myelogenous leukemia cells. *Cancer Res*. (2007) 67:5489–97. doi: 10.1158/0008-5472.CAN-07-0302
101. Bacigalupo A, Soracco M, Vassallo F, Abate M, Van Lint MT, Gualandi F, et al. Donor lymphocyte infusions (DLI) in patients with chronic myeloid leukemia following allogeneic bone marrow transplantation. *Bone Marrow Transplant*, 1997; 19: 927–32. doi: 10.1038/sj.bmt.1700762.
102. Christiansson L, Soderlund S, Svensson E, Mustjoki S, Bengtsson M, Simonsson B, et al. Increased level of myeloid-derived suppressor cells, programmed death receptor ligand 1/programmed death receptor 1, and soluble CD25 in Sokal high risk chronic myeloid leukemia. *PLoS ONE*, 2013; 8: e55818. doi: 10.1371/journal.pone.0055818.
103. Prost S, Relouzat F, Spentchian M, Ouzegdouh Y, Saliba J, Massonnet G, et al. Erosion of the chronic myeloid leukaemia stem cell pool by PPARgamma agonists. *Nature*, 2015; 525: 380–3. doi: 10.1038/nature15248.
104. Herrmann H, Sadovnik I, Cerny-Reiterer S, Rulicke T, Stefanzl G, Willmann M, et al. Dipeptidylpeptidase IV (CD26) defines leukemic stem cells (LSC) in chronic myeloid leukemia. *Blood*, 2014; 123: 3951–62. doi: 10.1182/blood-2013-10-536078.
105. Nabhan C, Rosen ST. Chronic lymphocytic leukemia: a clinical review. *JAMA*, 2014 Dec 3; 312(21): 2265-76. [Medline].
106. Bosch F, Ferrer A, Villamor N, et al. Fludarabine, cyclophosphamide, and mitoxantrone as initial therapy of chronic lymphocytic leukemia: high response rate and disease eradication. *Clin Cancer Res*, 2008 Jan 1; 14(1): 155-61. [Medline].
107. Byrd JC, Gribben JG, Peterson BL, et al. Select high-risk genetic features predict earlier progression following chemoimmunotherapy with fludarabine and rituximab in chronic lymphocytic leukemia: justification for risk-adapted therapy. *J Clin Oncol*, 2006 Jan 20; 24(3): 437-43. [Medline].
108. Wierda WG, O'Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. *J Clin Oncol*, 2011 Nov 1; 29(31): 4088-95. [Medline].
109. Robak T, Jamroziak K, Gora-Tybor J, et al. Comparison of cladribine plus cyclophosphamide with fludarabine plus cyclophosphamide as first-line therapy for chronic lymphocytic leukemia: a phase III randomized study by the Polish Adult Leukemia Group (PALG-CLL3 Study). *J Clin Oncol*, 2010 Apr 10; 28(11): 1863-9. [Medline].
110. Castellino AM. 'Possibility of Cure' for Some Patients With CLL. Medscape Medical News. Available at https://www.medscape.com/viewarticle/918027. September 10, 2019; Accessed: September 13, 2019.
111. Knauf WU, Lissitchkov T, Aldaoud A, Liberati AM, Loscertales J, Herbrecht R, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. *Br J Haematol*, 2012 Oct; 159(1): 67-77. [Medline].
112. Nabhan C, Coutré S, Hillmen P. Minimal residual disease in chronic lymphocytic leukaemia: is it ready for primetime?. *Br J Haematol*, 2007 Feb; 136(3): 379-92. [Medline].
113. Sayala HA, Rawstron AC, Hillmen P. Minimal residual disease assessment in chronic lymphocytic leukaemia. *Best Pract Res Clin Haematol*, 2007 Sep; 20(3): 499-512. [Medline].
114. Parikh SA, Keating MJ, O'Brien S, et al. Frontline chemoimmunotherapy with fludarabine, cyclophosphamide, alemtuzumab, and rituximab for high-risk chronic lymphocytic leukemia. *Blood*, 2011 Aug 25; 118(8): 2062-8. [Medline].
115. Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. *Blood*, 2011 Aug 25; 118(8): 2085-93. [Medline].
116. Skoetz N, Bauer K, Elter T, Monsef I, Roloff V, Hallek M, et al. Alemtuzumab for patients with chronic lymphocytic leukaemia. *Cochrane Database Syst Rev*, 2012 Feb 15. CD008078. [Medline]. [Full Text].
117. Awan FT, Hillmen P, Hellmann A, Robak T, Hughes SG, Trone D, et al. A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab versus fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia. *Br J Haematol*, 2014 Nov; 167(4): 466-77. [Medline].
118. Lemery SJ, Zhang J, Rothmann MD, Yang J, Earp J, Zhao H. U.S. Food and Drug Administration approval: ofatumumab for the treatment of patients

with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. *Clin Cancer Res*, 2010 Sep 1; 16(17): 4331-8. [Medline].
119. Nelson R. FDA Grants Full Approval to Ofatumumab (Arzerra) for CLL. Medscape Medical News. Available at http://www.medscape.com/viewarticle/823837. Accessed: March 10, 2016.
120. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*, 2014 Mar 13; 370(11): 997-1007. [Medline]. [Full Text].
121. van Oers MH, Kuliczkowski K, Smolej L, Petrini M, Offner F, Grosicki S, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncol*, 2015 Oct; 16(13): 1370-9. [Medline].
122. Robak, T, Warzocha, K, Babu, KG, et al. Health-Related Quality of Life and Patient-Reported Outcomes in Patients Receiving Ofatumumab in Combination with Fludarabine and Cyclophosphamide (FC) Versus FC Alone in the Complement 2 Trial. *Blood*, 2015; 126(23): 5288. [Full Text].
123. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*, 2014 Mar 20; 370(12): 1101-10. [Medline]. [Full Text].
124. McCall B. Obinutuzumab Active in Elderly Chronic Lymphocytic Leukemia. Medscape Medical News from the 18th Congress of the European Hematology Association (EHA). Available at http://www.medscape.com/viewarticle/806700. June 21, 2013; Accessed: October 21, 2019.
125. Flinn IW, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*, 2018 Dec 6; 132(23): 2446-2455. [Medline].
126. Mougalian SS, O'Brien S. Adverse prognostic features in chronic lymphocytic leukemia. *Oncology (Williston Park)*, 2011 Jul; 25(8): 692-6, 699. [Medline].
127. Woyach JA, Ruppert AS, Heerema NA, Peterson BL, Gribben JG, Morrison VA, et al. Chemoimmunotherapy With Fludarabine and Rituximab Produces Extended Overall Survival and Progression-Free Survival in Chronic Lymphocytic Leukemia: Long-Term Follow-Up of CALGB Study 9712. *J Clin Oncol*, 2011 Apr 1; 29(10): 1349-55. [Medline].
128. Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol*, 2010 Apr 1; 28(10): 1756-65. [Medline].
129. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010 Oct 2; 376(9747): 1164-74. [Medline].
130. Elter T, Gercheva-Kyuchukova L, Pylylpenko H, Robak T, Jaksic B, Rekhtman G, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. *Lancet Oncol*, 2011 Dec; 12(13): 1204-13. [Medline]. [Full Text].
131. Nelson R. New Drug Combo Potentially 'Practice Changing' in CLL. Medscape [serial online]. Available at http://www.medscape.com/viewarticle/817454. Accessed: December 16, 2013.
132. González-Rodríguez AP, Payer AR, Acebes-Huerta A, Huergo-Zapico L, Villa-Alvarez M, Gonzalez-García E, et al. Lenalidomide and chronic lymphocytic leukemia. *Biomed Res Int*, 2013. 2013: 932010. [Medline]. [Full Text].
133. Venclexta (venetoclax) [package insert]. North Chicago, IL: AbbVie, Inc. May 2019. Available at [Full Text].
134. Venclexta (venetoclax) [package insert]. North Chicago, IL: AbbVie, Inc. May 2019. Available at [Full Text].