The effectiveness of ibrutinib in chronic lymphocytic leukaemia: a nationwide, population-based study in the Netherlands.

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The effectiveness of ibrutinib in chronic lymphocytic leukaemia: a nationwide, population-based study in the Netherlands.
Br J Haematol. 2020 Jan 28;:
Authors: van der Straten L, Levin MD, Visser O, Blijlevens NMA, Cornelissen JJ, Doorduijn JK, Kater AP, Dinmohamed AG
PMID: 31991479 [PubMed — as supplied by publisher]

Daratumumab prevents programmed death ligand-1 expression on antigen-presenting cells in de novo multiple myeloma.

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Daratumumab prevents programmed death ligand-1 expression on antigen-presenting cells in de novo multiple myeloma.
Cancer Med. 2020 Jan 28;:
Authors: Stocker N, Gaugler B, Ricard L, de Vassoigne F, Marjanovic Z, Mohty M, Malard F
Abstract
BACKGROUND: Daratumumab (Dara), an anti-CD38 monoclonal antibody, has an immunologic mechanism of action through targeting of CD38 expressing immune cells in patients with multiple myeloma (MM). Furthermore, it was recently shown that CD38 upregulation in tumors, is a major mechanism of acquired resistance to antiprogrammed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1). Therefore, we decided to evaluate the immunomodulatory effects of CD38 blockade by Dara on the PD-L1 expressing immune cells.
METHODS: We analyzed CD38 and PD-L1 expression on immune cells at different time points in 18 newly diagnosed MM receiving bortezomib, lenalidomide and dexamethasone, with or without Dara.
RESULTS: We first confirmed that CD38 is widely expressed on immune cells, with the strongest expression on plasmacytoid dendritic cells (pDC). Furthermore, Dara induces a strong depletion of pDC in addition to the well-known rapid depletion of natural killer cells. Finally, we found that PD-L1 expression on antigen-presenting cells (APC) increases with MM treatment in patients that did not received Dara, while addition of Dara prevents this increase.
CONCLUSION: Overall, our results suggest new mechanisms of action of Dara through depletion of pDC and prevention of PD-L1 upregulation expression on APC. Our finding provides new evidences for development of therapeutic strategies targeting both CD38 and PD-L1/PD-1 pathway in patients with MM.
PMID: 31991058 [PubMed — as supplied by publisher]

Current Status of Chimeric Antigen Receptor T-Cell Therapy in Multiple Myeloma.

Related Articles
Current Status of Chimeric Antigen Receptor T-Cell Therapy in Multiple Myeloma.
Am J Clin Oncol. 2020 Jan 27;:
Authors: Jindal V, Khoury J, Gupta R, Jaiyesimi I
Abstract
Multiple myeloma (MM) is an incurable malignancy of plasma cells. Recently multiple new therapeutic options have been introduced which was able to improve overall survival but ultimately patient become refractory specifically in patients with poor cytogenetics. Therefore, novel therapeutic options like immunotherapy are needed to improve outcomes. Chimeric antigen receptor (CAR) T-cell therapy is immunotherapy in which T cell are genetically engineered against a tumor-specific antigen and transfused back to the patient to mount major histocompatibility complex-independent cancer-specific immune response. The success of CAR T-cell therapy in lymphoid malignancies encouraged its development in MM. Most of the clinical studies target B-cell maturation antigen in relapsed refractory MM and relapse is the major issue. In this article, we will present the basics of CAR T-cell therapy, the most recent clinical and preclinical data, and we will discuss the future therapeutic realm of CAR T cells in MM.
Standardizing Chemotherapy Regimen Nomenclature: A Proposal and Evaluation of the HemOnc and National Cancer Institute Thesaurus Regimen Content.

Abstract
PURPOSE: Due to decades of nonstandardized approaches to the naming of chemotherapy regimens, representation in electronic health records and secondary systems is highly variable. This hampers efforts to understand patterns of chemotherapy usage at the population level. In this article, we describe a proposal for rules to standardize the nomenclature of chemotherapy regimens and illustrate applications of these rules.

METHODS: Through our experience with building HemOnc.org, which has been under construction since 2011, we formulated a set of guidelines and recommendations for the standard representation of chemotherapy regimen names. We then performed a mapping between the HemOnc and National Cancer Institute Thesaurus vocabulary's regimens and evaluated conformance with the naming conventions. Finally, we assembled a database of acronyms and names for multiple myeloma regimens to illustrate the scope of the problem.

RESULTS: For the first use case, 242 of 527 (45.1%) of the regimen names differed. The schema was able to allocate a preferred source for 217 (89.4%) of these regimens. For the second use case, we expanded 130 multiple myeloma regimens to 1,138 unique regimen names and demonstrate ways in which the schema can collapse these into disambiguated, but abbreviated, regimen names.

CONCLUSION: To our knowledge, this is the first proposal to normalize chemotherapy regimen nomenclature. If our recommendations are adopted, we expect that the uniformity of treatment exposure representation in hematology/oncology will increase, which will enable large-scale efforts such as ASCO's CancerLinQ to achieve better standardization.

PMID: 31990758 [PubMed — as supplied by publisher]

Long-term outcomes after autologous stem cell transplantation for multiple myeloma.

Abstract
As multiple myeloma (MM) treatments evolve, frequent updates are required to monitor the long-term effect of changes in approach. Traditionally, MM is considered an incurable disease, with most patients eventually relapsing. However, improvements in treatments have raised the possibility that MM might be functionally curable. To examine improvements in long-term survival, we followed 4329 patients with newly diagnosed MM treated with autologous stem cell transplantation (ASCT) at the University of Arkansas for Medical Sciences from 1989 through 2018. Overall survival (OS) and progression-free survival (PFS) were evaluated using Kaplan-Meier analysis, Cox proportional hazards models, relative survival analysis, and cure modeling among different time periods, risk groups, and demographic traits. Steady improvements in OS were found, with patients treated in 2014 or later having superior OS (hazard ratio, 0.35; 95% confidence interval [CI], 0.27−0.45) and reduced excess risk for MM death (relative excess risk, 0.30; 95% CI, 0.22−0.41) compared with patients treated in 1997 or earlier. Patients treated during intervening time periods often had intermediate survival, but trends in OS, PFS, and landmarked analyses were inconsistent. Cure models support the potential for cure, ranging from 6.3% to 31.3%, depending on the year of treatment, with 10.0% to 18.6% of patients achieving their normal life expectancy across multiple periods. There was some evidence of reductions in early mortality within 3 years of diagnosis, longer complete response (CR) duration, and reductions in relapse after achieving CR. However, results differed depending on age, risk group, and cytogenetic characteristics.

PMID: 31990333 [PubMed — in process]

Related Articles
Standardizing Chemotherapy Regimen Nomenclature: A Proposal and Evaluation of the HemOnc and National Cancer Institute Thesaurus Regimen Content.

PMID: 31990580 [PubMed — in process]
Deep profiling of apoptotic pathways with mass cytometry identifies a synergistic drug combination for killing myeloma cells.

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Deep profiling of apoptotic pathways with mass cytometry identifies a synergistic drug combination for killing myeloma cells.

Cell Death Differ. 2020 Jan 27;

Authors: Teh CE, Gong JN, Segal D, Tan T, Vandenberg CJ, Fedele PL, Low MSY, Grigoriadis G, Harrison SJ, Strasser A, Roberts AW, Huang DCS, Nolan GP, Gray DHD, Ko ME

Abstract

Multiple myeloma is an incurable and fatal cancer of immunoglobulin-secreting plasma cells. Most conventional therapies aim to induce apoptosis in myeloma cells but resistance to these drugs often arises and drives relapse. In this study, we sought to identify the best adjunct targets to kill myeloma cells resistant to conventional therapies using deep profiling by mass cytometry (CyTOF). We validated probes to simultaneously detect 26 regulators of cell death, mitosis, cell signaling, and cancer-related pathways at the single-cell level following treatment of myeloma cells with dexamethasone or bortezomib. Time-resolved visualization algorithms and machine learning random forest models (RFMs) delineated putative cell death trajectories and a hierarchy of parameters that specified myeloma cell survival versus apoptosis following treatment. Among these parameters, increased amounts of phosphorylated cAMP response element-binding protein (CREB) and the pro-survival protein, MCL-1, were defining features of cells surviving drug treatment. Importantly, the RFM prediction that the combination of an MCL-1 inhibitor with dexamethasone would elicit potent, synergistic killing of myeloma cells was validated in other cell lines, in vivo preclinical models and primary myeloma samples from patients. The level of miR-15a was downregulated in MM cells and correlated with inferior outcome of MM patients. In the present study, we first developed an oligo-single-stranded DNA mimicking the sequence of hsa-miR-15a-5p (OMM-15a) and modified with locked nucleic acid (LNA-15a) to evaluate its anti-MM effects. Our results indicated that the LNA-15a presented an exciting anti-MM effect that showed notable cell growth suppression and apoptosis promotion in MM and other cancer cell lines through downregulating the expression level of target genes BCL-2, VEGF-A, and PHF19. Moreover, LNA-15a treatment significantly improved the anti-MM activity of bortezomib with the synergism effect in OCI-My5 MM cells. In our in vivo study, LNA-15a treatment significantly suppressed the tumor growth, and prolonged the survival of mice compared with the control group. However, our results indicated that the native form of oligo-single-stranded DNA mimic of hsa-miR-15a-5p (OMM-15a) without any modification had no effective inhibition on cell growth, even after increasing the dosage of OMM-15a in the treatment. Altogether, our finding provides the preclinical rationale to support the oligo-single-stranded DNA mimic of hsa-miR-15a with LNA modification, which is a promising tool for the therapy of both MM and other tumors with miR-15a downregulation.

PMID: 31988477 [PubMed — as supplied by publisher]

BRAF and DIS3 Mutations Associate with Adverse Outcome in a Long-term Follow-up of Patients with Multiple Myeloma.

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BRAF and DIS3 Mutations Associate with Adverse Outcome in a Long-term Follow-up of Patients with Multiple Myeloma.

Clin Cancer Res. 2020 Jan 27;


Abstract

Therapeutic effects of oligo-single-stranded DNA mimicking of hsa-miR-15a-5p on multiple myeloma.

Related Articles

Therapeutic effects of oligo-single-stranded DNA mimicking of hsa-miR-15a-5p on multiple myeloma.
PURPOSE: Copy number changes and translocations have been studied extensively in many datasets with long term follow-up. The impact of mutations remains debated given the short time to follow-up of most datasets.

METHODS: We performed targeted panel sequencing covering 125 myeloma-specific genes and the loci involved in translocations in 223 newly diagnosed myeloma samples recruited into one of the Total Therapy Trials (TT).

RESULTS: As expected, the most commonly mutated genes were NRAS, KRAS, and BRAF making up 44% of patients. Double-Hit, BRAF and DIS3 mutations had an impact on outcome alongside classical risk factors in the context of an intensive treatment approach. We were able to identify both V600E and non-V600E BRAF mutations, 58% of which were predicted to be hypoactive or kinase dead. Interestingly, 44% of the hypoactive/kine dead BRAF mutated patients showed co-occurring alterations in KRAS, NRAS or activating BRAF mutations suggesting they play a role in the oncogenesis of multiple myeloma (MM) by facilitating MAPK activation and may lead to chemoresistance.

CONCLUSION: Overall, these data highlight the importance of mutational screening to better understand newly diagnosed MM (NDMM) and may lead to patient specific mutation-driven treatment approaches.

PMID: 31988198 [PubMed — as supplied by publisher]

Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management.

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Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management.

Am J Hematol. 2019 06;94(6):710–725

Authors: Jain P, Wang M

Abstract

Unprecedented advances in our understanding of the pathobiology, prognostication, and therapeutic options in mantle cell lymphoma (MCL) have taken place in the last few years. Heterogeneity in the clinical course of MCL-indolent vs aggressive-is further delineated by a correlation with the mutational status of the variable region of immunoglobulin heavy chain, methylation status, and SOX-11 expression. Cyclin-D1 negative MCL, in situ MCL neoplasia, and impact of the karyotype on prognosis are distinguished. Apart from Ki-67% and morphology pattern (classic vs blastoid/pleomorphic), the proliferation gene signature has helped to further refine prognostication. Studies focusing on mutational dynamics and clonal evolution on Bruton’s tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib) and/or Bcl2 antagonists (venetoclax) have further clarified the prognostic impact of somatic mutations in TP53, BIRC3, CDKN2A, MAP3K14, NOTCH2, NSD2, and SMARCA4 genes. In therapy, long-term follow-up on chemo-immunotherapy studies has demonstrated durable remissions in some patients; however, long-term toxicities, especially from second cancers, are a serious concern with
chemotherapy. The therapeutic options in MCL are constantly evolving, with dramatic responses from nonchemotherapeutic agents (ibrutinib, acalabrutinib, and venetoclax). Chimeric antigen receptor therapy and combinations of nonchemotherapeutic agents are actively being studied and our focus is shifting toward making the treatment of MCL chemotherapy-free. Still, MCL remains incurable. The following aspects of MCL continue to pose a challenge: disease transformation, role of the cytokine-microenvironmental milieu, incorporation of positron emission tomography-computerized tomography imaging, minimal residual disease in the prognosis, circulating tumor DNA testing for clonal evolution, predicting resistance to BTK inhibitors, and optimal management of patients who progress on BTK/Bcl2 inhibitors. Next-generation clinical trials should incorporate nonchemotherapeutic agents and personalize the treatment based upon the genomic profile of individual patient. Recent advances in the field of MCL are reviewed.

PMID: 30963600 [PubMed — indexed for MEDLINE]

Integration of transcriptional and mutational data simplifies the stratification of peripheral T-cell lymphoma.

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Integration of transcriptional and mutational data simplifies the stratification of peripheral T-cell lymphoma.


Abstract

The histological diagnosis of peripheral T-cell lymphoma (PTCL) can represent a challenge, particularly in the case of closely related entities such as angioimmunoblastic T-lymphoma (AITL), PTCL-not otherwise specified (PTCL-NOS), and ALK-negative anaplastic large-cell lymphoma (ALCL). Although gene expression profiling and next generations sequencing have been proven to define specific features recurrently associated with distinct entities, genomic-based stratifications have not yet led to definitive diagnostic criteria and/or entered into the routine clinical practice. Herein, to improve the current molecular classification between AITL and PTCL-NOS, we analyzed the transcriptional profiles from 503 PTCLs stratified according to their molecular configuration and integrated them with genomic data of recurrently mutated genes (RHOA G17V, TET2, IDH2 R172, and DNMT3A) in 53 cases (39 AITLs and 14 PTCL-NOSs) included in the series. Our analysis unraveled that the mutational status of RHOA G17V, TET2, and DNMT3A poorly correlated, individually, with peculiar transcriptional fingerprints. Conversely, in IDH2 R172 samples a strong transcriptional signature was identified that could act as a surrogate for mutational status. The integrated analysis of clinical, mutual, and molecular data led to a simplified 19-gene signature that retains high accuracy in differentiating the main nodal PTCL entities. The expression levels of those genes were confirmed in an independent cohort profiled by RNA-sequencing.

PMID: 30829413 [PubMed — indexed for MEDLINE]

Frontline antibiotic therapy for early-stage Helicobacter pylori-negative gastric MALT lymphoma.

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Frontline antibiotic therapy for early-stage Helicobacter pylori-negative gastric MALT lymphoma.


PMID: 30785215 [PubMed — indexed for MEDLINE]