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NASKAH SIMPOSIUM
RITUXIMAB IN THE TREATMENT OF
INDOLENT AND AGGRESSIVE NON-HODGKIN LYMPHOMAS

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Non-Hodgkin Lymphomas (NHL) represent a heterogenous group of lymphoid malignancies that arise from B-cell (85%), T-cell, and NK-cell (15%). NHL is the most frequent hematologic malignancies in the adults. WHO classification 2001, updated in 2008, based on morphology, cell lineage, immunophenotype, genetics, molecular, and clinical features. WHO classified malignant lymphoma into 5 categories: precursor B-cell neoplasms, mature B-cell neoplasms, precursor T-cell and NK-cell neoplasms, mature T-cell and NK-cell neoplasms, and Hodgkin lymphomas. Based on clinical behavior, NHL is subdivided into aggressive lymphomas and indolent lymphomas. Aggressive lymphomas are fast-growing, but are highly responsive to chemotherapy and more often curable. Indolent lymphomas represents a group of incurable, slow-growing lymphomas that are highly responsive to initial therapy but relapse with less responsive disease. Aggressive lymphomas include diffuse B-cell lymphoma (DLCB), mantle cell lymphoma (MCL), and Burkitt's lymphoma. Indolent lymphomas include follicular lymphoma (FL), marginal zone lymphoma (nodal, splenic, and MALT), and chronic lymphocytic leukemia/small lymphocytic lymphoma. The most frequent aggressive lymphoma is DLCB, constitutes 30% - 50% of NHL, and the most frequent indolent lymphoma is follicular lymphoma (FL) constitutes approximately 70% of indolent lymphoma and up to 25% of all cases of NHL.

Diagnosis of NHL should be made on the basis of surgical specimen/excisional lymphnode biopsy providing enough material. Immunohistochemistry (CD45, CD20 and CD3) is mandatory. A complete blood count, routine blood chemistry including LDH, uric acid and hepatitis B and C, as well as screening for HIV are required. Protein electrophoresis is recomended. Patients should have at least CT-scan of the chest and
abdomen, as well as bone marrow aspirate and biopsy. FDG-PET scanning is strongly recommended to fulfill the revised staging system (Lugano) and revised criteria of treatment response. Performance status and cardiac function should be assessed before treatment. The staging is established according to the Ann Arbor system (updated by Lugano staging). For prognostic purpose, IPI and age-adapted IPI should be calculated for aggressive lymphoma (DLBC), and FLIPI for follicular lymphoma.

There has been a revolution in the treatment of B-cell non-Hodgkin lymphoma, owing largely to the availability of therapeutic monoclonal antibody. Rituximab was the first widely adopted monoclonal antibody approved for cancer treatment. Rituximab (Mabthera/Rituxan, Roche) is a chimeric IgG1 monoclonal antibody directed against CD20 surface antigen found on most normal and neoplastic B lymphocyte. Rituximab kill tumor cells through antibody-dependent cellular toxicity, complement-dependent cytotoxicity, and induction of apoptosis.

DLBC Lymphoma is the most common aggressive lymphoma account for more than 30% NHL. Treatment options for DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (stage III-IV), risk score (IPI), and age of patients. CHOP (cyclophosphamid, doxorubicin, oncovin, prednison) regimen remained the gold standard therapy for DLCBL. The addition of more chemotherapy drugs into complex regimens (m-BACOD, proMACE-CytaBOM, MACOP-B) showed no increase of efficacy. For DLCBL stage I-II, NCCN recommend 3 cycles of CHOP followed by involved field radiation therapy (IFRT). The better efficacy of addition of rituximab to the CHOP and IFRT (R-CHOP) has been reported in patients with limited stage DLCBL. In the SWOG 0014 study that evaluated 3 cycles of R-CHOP followed by IFRT, the 4-year OS rate was 92%. In historical comparison, these results were favourable relative to the survival rate for patients without rituximab. Mabthera International Trial (MlnT) had evaluated 6 cycles of CHOP-like chemotherapy to 6 cycles of CHOP-like chemotherapy plus rituximab. The trial found a benefit to rituximab containing regimen with a 6-year OS rate (90.1% vs 80%), 6-year EFS rate (74.3% vs 55.8%), and PFS rate (80.2% vs 63.9%). Based on those studies, R-CHOP 21 chemotherapy has been recommended as the standard treatment in DLCBL stage III-IV (advanced stage). Long-term follow up of this study showed a consistent results: PFS (36.5% vs 20%),
DFS (64% vs 43%), and OS (43.5% vs 28%). These findings have been confirmed in three additional randomized trial. In the RICOVER 60 trial, the addition of rituximab to dose-dense CHOP significantly improved clinical outcome in elderly patients. But in two randomized trial comparing R-CHOP-21 with dose-dense R-CHOP-14 found no significant difference in either PFS or OS. The ECOG/CALGB 9703 study showed that maintenance rituximab in first remission offered no clinical benefit to patients who received R-CHOP as their induction therapy. ESMO (European Society of Medical Oncology) Clinical Practice Guidelines stated that R-CHOP-21 six to eight doses, is the current standard for CD20+ DLBCL of all stage (category I,A). NCCN (National Comprehensive Cancer Network) recommendations are: (1) for patients with non bulky (<10cm) stage I or II disease, R-CHOP (3 cycles) with IFRT or R-CHOP (6 cycles) with or without IFRT is recommended ; (2) IFRT is recommended for patients who are not candidate for chemotherapy; (3) patients with bulky disease (≥10 cm) may be more efficiently treated with 6 cycles of R-CHOP with or without locoregional RT (category 1). For patients with advanced disease, the recommended treatment is R-CHOP-21 (category 1). In selected cases, RT to bulky sites may be beneficial (category 2). R-CHOP-21 is recommended as initial therapy, however, other comparable regimens may be also acceptable in selected circumstances. Suggested alternate options include dose–adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) plus rituximab (category 2B) or dose-dense R-CHOP-14 (category 3). For relapsed and refractory DLBCL, HDT/ASCR is the treatment of choice. Second-line treatment for relapsed/refractory patients are DHAP (cisplatin, cytosine arabinoside, dexamethason), ICE (ifosfamide, carboplatin, etoposide), ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin), GDP (gemcitabine, dexamethasone, cisplatin), GemOx (gemcitabine, oxaliplatin), MINE (mitoxantrone, ifosfamid, mesna, etoposide) with or without rituximab (depending or wether the patient is deemed to be refractory to prior rituximab regimens).

Follicular lymphoma (FL) is the most frequent indolent lymphomas subtype, accounting for 10% to 20% of all NHL. Less than 10% patients with FL have early stage (stage I/II), the majority of patients have advanced stage (III/IV). Early stage FL patients do not require immediate treatment
unless they have symptomatic nodal disease, compromised end-organ function, B symptoms, symptomatic extranodal disease or cytopenias. In symptomatic FL, rituximab has had a large impact on the treatment of FL. Its effectiveness as a single agent and in conjunction with known chemotheraphy regimens has made it a standard of care in the treatment of FL. For patients with Stage I-II disease, NCCN recommended involved-site radiotherapy (ISRT: 24-30 GY), with an additional 6 GY for selected patients with bulky disease. Alternate treatment options include immunotherapy with or without chemotherapy (category 2B). For advanced disease (III/IV) treatment should only be initiated when indicated by GELF criteria {symptoms attributable to FL, threatened end-organ function, cytopenias secondary to lymphoma, bulky disease (single mass > 7 cm or 3 or more masses > 3 cm), splenomegaly, and steady progression over at least 6 months}. The most commonly prescribed chemotherapy is rituximab combination with CHOP (R-CHOP), CVP (R-CVP) or bendamustine (BR), as the first-line treatment in patients with advanced stage FL (category 1). Bendamustine-Rituximab (BR) regimen has been shown to have less toxicity and superior to FFP compared to R-CHOP, however, the OS outcome were not significantly different. Single agent rituximab is the preferred first-line therapy in elderly or infirm patients. In relapsed or progressive disease, should be histologically documented to exclude transformation to DLBCL. For patients requiring second-line therapy or treatment for disease unresponsive to first-line regimens, the options include other chemoimmunotherapy regimens used for first-line treatment, BVR (bendamustine, bortezomid, rituximab), fludarabine combined with rituximab, FCMR regimen (category 1), RIT (category 1) or any of the second-line used for patients with DLCBL.

Monitoring of side effects of chemoimmunotherapy are very important. Tumor lysis syndrome (TLS) is a potentially serious complication, especially in high dose chemotherapy and high tumor burden. TLS characterized by metabolic abnormalities caused by the abrupt release of intracellular content into the blood resulting from cellular disintegration induced by chemotherapy. It is usually observed within 12 to 72 hours after start of chemotherapy.

It can be concluded that, rituximab, immunotherapy anti-C20, give a very significant breakthrough in the management of NHL, in aggressive as
well as in indolent lymphomas. There are still many problems, such as: rituximab resistance and intolerance. Future research should be focused on development of new monoclonal antibodies, monoclonal antibodies linked to a radioisotope, new immunomodulatory agents, and novel drugs such as kinase inhibitors.
RECENT ADVANCES IN MANAGEMENT OF CHRONIC MYELOID LEUKEMIA

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm which characterized by the presence of Philadelphia chromosome (Ph) resulting from a reciprocal translocation between chromosome 9 and 22 \( \{t(9:22)\} \). This translocation results in the head-to-tail fusion of the break cluster region (BCR) gene on chromosome 22 and the Albeson murine leukemia (ABL1) gene located on chromosome 9. The product of BCR-ABL1 fusion gene, a fusion protein (p210) with deregulated tyrosine kinase activity, plays a central role in the pathogenesis of CML. BCR-ABL1 gene is a constitutively active tyrosine kinase that promote growth and replication through downstream pathways such as RAS, RAF, JUN kinase, MYC and STAT. This influences leukomegenesis by creating a cytokine-independent cell cycle with aberrant apoptotic signals in response to cytokine withdrawal.

The incidence of CML ranges between 1.0 and 1.5 cases/100,000/per year and accounts for around 15% of newly diagnosed leukemia in adults. The median age of disease onset is 67 years. In 2014, an estimated 5,980 people will be diagnosed with CML in United States, and 810 people will die from the disease.

CML can be classified into three disease phases: chronic phase (CML-CP), accelerated phase (CML-AP), and blast phase (CML-BP). The symptoms are not specific, including fatigue, weight loss, malaise, and left upper quadrant fullness or pain. Splenomegaly is the most consistent physical sign in CML, and is detected in 50-60% of cases. The hallmark of diagnosis is leucocytosis, usually > 20x10^9/L, with basophilia and immature granulocytes, mainly neutrophile, metamyelocyte and myelocyte. Blast in peripheral blood and bone marrow is < 5% in CP, 5-19% in AP and > 20% in BP. The diagnosis must be confirmed by cytogenetics showing \( t(9;22) \).
(Philadelphia chromosome), or BCR-ABL transcript by reverse transcriptase polymerase chain reaction (RT-PCR).

Historically, the treatment of CML begins with busulfan and hydroxyurea, but has undergone a profound evolution over a relatively short period of time, starting with allogeneic stem cell transplantation (allo SCT) and interferon and more recently and most significantly, with the tyrosine kinase inhibitor (TKI). Busulfan, that should no longer be used, then hydroxyurea, that is still used for a short and quick pretreatment phase in case of marked leucocytosis or thrombosis. Interferon-α became the gold standard in 1990s. Imatinib mesylate (Glevec-Novatis) was the first TKI to be used and is still the gold standard of first-line treatment of CML-CP. TKI therapy is superior to allo-SCT in first-line therapy of CML, because of transplant-related mortality. Imatinib is the first generation TKI. Next generation TKI (second and third generation), namely dasatinib, nilotinib, bosutinib, and ponatinib were then developed. IRIS study is considred a landmark clinical trial for TKI (comparing imatinib 400 mg vs interferon-α plus low-dose cytarabine). Major cytogenetic response and FFP (freedom from progression) were better in imatinib. The update of IRIS study has confirmed and extended the earlier results, reporting FFP survival 84% and OS (overall survival) 88% after 6 years. Based on this result, FDA approved imatinib 400 mg as first-line treatment of newly diagnosed CML. Currently two other TKIs available for clinical use, namely Nilotinib (Tasigna-Novatis) and Dasatinib (Sprycel-Bristol Myers Squibb). In ENESTnd study, two doses of imatinib (300 mg and 400 mg twice daily) were compared with imatinib 400 mg once daily. Major molecular response (MMR) was significantly higher for both doses of nilotinib compared with the imatinib group (44 and 43% vs 22%). In DASISION trial, imatinib 400 mg once daily compared with dasatinib 100 mg once daily in CML-CP. The CCyR (complete cytogenetic response) more frequently than dose on imatinib (77 vs 66%). Based on these data, FDA approved nilotinib and dasatinib as first-line treatment for newly diagnosed CML in chronic phase. ESMO (European Society of Medical Oncology), ELN (European Leukemia Network), and NCCN (National Comprehensive Cancer Network) recommend any of the three TKIs, imatinib (400 mg once daily), nilotinib (300 mg twice daily), and dasatinib (100 mg daily) as first-line treatment of newly diagnosed CML-CP. Although several studies reported nilotinib and
dasatinib give faster and deeper response, NCCN still considered imatinib (400 mg) as a reasonable first-line treatment of CML due to more evidence-based data are available on efficacy and side effects of this TKI. The choice of first-line therapy in a given patient may depend on risk score (Sokal or EUTOS), physician experience, age, ability to tolerate therapy, and the presence of comorbid conditions.

Monitoring of response of therapy is very important in the management of CML. Monitoring can be performed using hematologic (peripheral blood and bone marrow), cytogenetic (percentage of Ph chromosome in cell in metaphase) and molecular response (level of BCR-ABL transcript with quantitative-RT-PCR). The response of TKI can be classified as optimal, meaning that continuing treatment the survival is predicted to be normal or close to normal, and failure, meaning that treatment must be switched to a second generation TKI, or alloHSCT. Between optimal and failure, there is a grey zone that define as “warning”, meaning that the response must be monitored more carefully and that the patient may be eligible for potentially better treatments. The response of TKI is the most important prognostic factor. Optimal response is associated with the best long-term outcome – that is, with a duration of life comparable with that of the general population. The problems of TKIs therapy in CML are TKI resistance, intolerance due to side effects, and the cost of therapy. However, the use of TKIs in CML is a breakthrough in CML therapy, has dramatically improved outcome in patients with CML. It has become the standard of care for all patients with newly diagnosed CML.
RECOMBINANT FACTOR VIIA FOR MANAGEMENT OF HEMOPHILIA WITH INHIBITOR

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Introduction

Hemophilia A and B are hereditary X-chromosomal recessive disorders caused by deficiency or absence of coagulation factors VIII (FVIII) or IX (FIX), respectively. The incidence of hemophilia is commonly reported as 1 in 5000 male births or 1 in 10,000 of the general population. Hemophilia A is four times more common than hemophilia B. The disorders are classified according to the coagulation factor activity (FVIII:C or FIX:C, respectively) present in blood with three categories comprising severe (<1% of normal activity), moderate (1–5%) or mild (>5% to <40%). Although these categories define overall bleeding manifestations, the clinical phenotype may vary within each group. Mild hemophilia can go unnoticed depending on the level of deficiency and the stressors the individual experiences, therefore the proportion of cases of mild hemophilia that are registered may vary. Severe hemophilia is characterized by spontaneous joint, muscle, gastrointestinal and central nervous system (CNS) bleeding resulting in substantial morbidity and even mortality. However, hemophilia must sometimes be differentiated from other bleeding disorders when the family history is negative or unknown. Differentiation between hemophilia and other conditions, such as some types of von Willebrand disease or acquired factor inhibitors, and distinction between hemophilia A and B are crucial for appropriate management. Patients with hemophilia, particularly those with severe disease, develop bleeding episodes that are treated with replacement of the missing factor (ie, factor VIII or factor IX concentrates). A complication of hemophilia treatment is the development of an inhibitor, which usually occurs shortly after replacement therapy has been initiated. The inhibitors are antibodies (primarily IgG) directed against the specific deficient factor. Development of inhibitors is typically assessed in
relationship to the number of exposure days (ie, days on which the patient has received one or more doses of replacement factor).

**Inhibitors**

The development of inhibitors is more common in patients with hemophilia A than in those with hemophilia B. Many of the principles that apply to factor VIII inhibitors also apply to factor IX inhibitors. However, the development of inhibitors in factor IX deficiency may be associated with some specific manifestations including anaphylaxis and nephrotic syndrome. Inhibitors in both hemophilia A and B are more likely to form in patients with severe disease. The degree of response in Bethesda units has been used to further classify patients with factor VIII or IX inhibitors. High responders — Patients who develop titers above five Bethesda units at any time are considered high responders. Such patients show an increase in antibody titer after each exposure; this response begins within 2 to 3 days, peaks at 7 to 21 days, and may persist for years in the absence of re-exposure. Such high inhibitor levels render treatment with factor VIII preparations ineffective, and usually require bypassing the deficient clotting factor. Low responders — Low responders have persistently low antibody titers (less than five Bethesda units) that do not increase after factor infusion and may disappear. Such patients may continue to respond to treatment with factor VIII replacement therapy with minimal change in the factor VIII dose.

Factor VIII inhibitors have been reported in approximately 25 to 30 percent of patients with severe hemophilia A. They primarily occur early in treatment (eg, within the first 50 exposure days) in young children, and are much less common in patients with moderate and mild hemophilia A (3 to 13 percent). These relationships were illustrated in a study in which 95 children who were not previously exposed to factor VIII were treated with recombinant human factor VIII; the median follow-up was 1.5 years. Factor VIII inhibitors developed in 20 percent of patients after a median of nine days of exposure (which represented 15 months from initial treatment). The frequency of antibody development was 29 percent in the children with severe disease (factor VIII levels <2 percent of normal) and <10 percent in those with moderate to mild disease.
Predisposing factors

Both host and product factors influence the likelihood of inhibitor formation. Research continues to define the best predictors of inhibitor formation, as well as methods to decrease or prevent formation.

Severity of hemophilia — The predilection for patients with severe disease is consistent with observations that inhibitors primarily occur in patients with large deletions and stop mutations, compared with small deletions or missense mutations. There is a modest increase in antibody formation in patients with gene inversions.

Age — Patient age at the time of initial replacement treatment, treatment intensity, and the early use of prophylaxis may influence inhibitor formation.

Race — Race is also a factor in inhibitor development, with inhibitor formation in people of color about twice that of whites.

Replacement product — Factor VIII replacement products include plasma-derived and recombinant preparations. These products differ in their composition, purity, and potential contaminants.

Immunologic factors — Development of inhibitors is an immune phenomenon, and some data have suggested that immunologic factors may contribute to inhibitor development. As an example, the Hemophilia Inhibitor Genetics Study (HIGS) evaluated genes involved in immune regulation among 104 sibling pairs with hemophilia A who were discordant in inhibitor status. As siblings, these individuals had the same factor VIII mutation. Analysis of single nucleotide polymorphisms (SNPs) demonstrated variations in 13 immune response/immune modifier genes that correlated with inhibitor development.

Risk score

Findings from a cohort of consecutive previously untreated patients with severe hemophilia A (the CANAL study) were used to develop a risk score for the development of factor VIII inhibitors, which included the following adverse risk factors:

- Family history of inhibitors — 2 points
- High-risk gene mutation present — 2 points
- Intensive treatment at first bleeding episode — 3 points
In the training cohort (332 patients), inhibitor incidence was 6, 23, and 57 percent for those with a risk score of zero, 2, or ≥3 points, respectively. Similar incidences were noted in a validation cohort of 64 patients.

**Treatment**

Comprehensive Hemophilia Treatment Centers provide expertise for these specialized patients and should be consulted for the development of any treatment plan in a hemophilic patient with an inhibitor. The two components to therapy are treatment of active bleeding and inhibitor ablation via immune tolerance induction. In a review from Finland, for example, the annual death rate among such patients fell from 42 to 5.8 per thousand patient years in the periods 1970-1979 and 1980-1989, respectively.

**Recombinant FVIIa**

Recombinant FVIIa (rFVIIa, NovoSeven), produced and developed as a commercial product by NovoNordisk, was shown to be effective as a bypassing agent in hemophiliaics with inhibitors and in acquired hemophilia. It appeared to require doses up to 100 mcg/kg for efficacy, with no evidence of systemic activation of coagulation.

**Mechanism of action**

High-dose rFVIIa was originally thought to act by increasing the activity of the extrinsic tissue factor (TF)-associated coagulation pathway. However, the concentrations of rFVIIa required for hemostatic efficacy were far greater than would be required to saturate TF. This fact, combined with findings in experimental models has lent increasing support to the theory that rFVIIa does not exert its therapeutic effect through the TF pathway. Nonetheless binding of FVIIa to platelets appears to involve the glycoprotein Ib/IX/V complex and anionic phospholipids expressed on activated platelets. In the case of the hemophilias, platelet-bound rFVIIa partially restores platelet surface FX activation, which is deficient because of the absence of factor VIIIa/IXa complexes. In non-hemophilic conditions, platelet-bound rFVIIa increases activation of both FIX and FX and increases thrombin generation above normal levels. Increased thrombin generation then promotes increased activation and local accumulation of
platelets including dysfunctional platelets, potentially improving hemostasis in a wide range of bleeding conditions.

**Conditions affecting rFVIIa activity.**

Reduced levels of other coagulation factors and co-factors (eg, calcium, fibrinogen, prothrombin, factor X) as well as platelet number and function may limit the effectiveness of rFVIIa. Changes in body temperature and pH may reduce the activity of factor VIIa. While overall hemostatic function is impaired by hypothermia, rFVIIa may be effective even in patients whose body temperature cannot be normalized. The half-life of rFVIIa in the circulation is 2 hours, shorter than that of normal factor VII (4 to 6 hours), as well as that of most of the other coagulation factors.

**The use of recombinant human factor VIIa in hemophilia with inhibitors**

Recombinant human factor VIIa produces an excellent or effective response in over 90 percent of patients with hemophilia and inhibitors. Since licensure, the standard dosing has been considered to be 90 to 120 mcg/kg every 2 to 3 hours until cessation of bleeding. However, dosing levels, intervals, and duration of treatment are subject to considerable variation among different medical centers. In order to overcome the logistic difficulties of repeated frequent bolus injections and, in an attempt to minimize usage, administration of rFVIIa by continuous infusion has been utilized. Treatment regimens combining an initial bolus dose with subsequent continuous infusion have also been described. While clearly more convenient, there is no evidence that continuous infusion uses less drug to control bleeding. Indeed, there is uncertainty as to whether the continuous infusion of rFVIIa is as therapeutically effective as an equivalent total dose administered via bolus injection.

The proposed mechanism of action of rFVIIa suggests that intermittently attaining a high level of rFVIIa with bolus dosing will yield larger bursts of platelet-surface thrombin generation than will continuous maintenance of a lower plasma concentration. This has led some practitioners to advocate the use of higher, less frequent dosing of rFVIIa. Accumulating anecdotal evidence suggests that this approach is at least as effective as standard dosing, but there is very little relevant high quality data to support this position.
Dosing and laboratory monitoring

There is currently no means of determining the optimal dose and dosing regimen of rFVIIa for a given individual or a given condition, and clinical practices vary widely [91]. Since there is no laboratory test that correlates well with the clinical efficacy of rFVIIa, dosing must be determined empirically. While significant concern over the possibility of inciting thrombosis accompanied the initial use of rFVIIa, its subsequent safety record in treating hemophiliacs with inhibitors is impressive, with doses of up to 346 mcg/kg being well tolerated. Available clinical evidence suggests that the isolated thrombotic events associated with its use in approved indications occur primarily in subjects with pre-existing risk factors for thrombosis.

References


NEW INSIGHT IN MANAGEMENT OF NEUTROPENIA
Focus : Role of Growth Factors

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Introduction
Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria and/or fungi that translocate across intestinal mucosal surfaces. Cytotoxic chemotherapy can cause profound and sometimes prolonged neutropenia, which may result in hospitalization for treatment of fever or cause potentially fatal infection. Although profound prolonged neutropenia is most likely in the pre-engraftment phase of hematopoietic cell transplantation (HCT, particularly allogeneic) and in patients undergoing induction therapy for acute leukemia, chemotherapy-related neutropenia can also occur in patients receiving standard-dose chemotherapy for other neoplasms.

Neutropenia
The definition of neutropenia varies from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 cells/µL, and severe neutropenia is usually defined as an ANC <500 cells/µL, or an ANC that is expected to decrease to <500 cells/µL over the next 48 hours. The risk of clinically important infection rises as the neutrophil count falls below 500 cells/µL and is higher in those with a prolonged duration of neutropenia (>7 days). The definition of fever as an indicator of infection in neutropenic patients has varied. Despite the observation that there is a range of normal body temperatures, in one survey, a majority (75 percent) of 270 medical professionals reported that normal body temperature is 37°C (98.6°F). A survey of members of the British Society for Haematology regarding their institutional definitions of fever identified 10 definitions of fever, ranging from a single temperature >37.5°C to either a single temperature >39°C or two successive
temperatures >38.4°C. These beliefs notwithstanding, the empirically observed mean oral temperature of 148 healthy adults between ages 18 and 40 years was reported as 36.8±0.4°C (98.2±0.7°F) with a range of 35.6°C (96.0°F) to 38.2°C (100.8°F), the latter defining the upper limit of normal. The Infectious Diseases Society of America defines fever in neutropenic patients as a single oral temperature of >38.3°C (101°F) or a temperature of >38.0°C (100.4°F) sustained for >1 hour.

Neutrophils play an important role in the host defense against bacterial invasion. Primarily they act by prevention and containment of bacterial and fungal infections. In addition they are important mediators of inflammatory responses. Approximately 1 • 10⁹ neutrophils/kg are produced in the bone marrow daily. Major characteristics of these neutrophils are the potential to travel through the body to sites of injury, to phagocytose and destroy the intruders. Neutropenia (generally defined as an absolute granulocyte count of <500/mm³) can be divided into disorders secondary to abnormalities of production, distribution, or secondary to rapid use or turnover of cells in peripheral blood. Of these, production anomalies are the most frequent. A more helpful classification based on production problems classifies neutropenia in forms related to intrinsic hematological disorders and secondary forms caused by extrinsic factors, including drugs, radiation, autoimmune disorders, and infections. Drug-induced neutropenia is probably the most frequent cause of neutropenia. As radiotherapy, cytotoxic drugs predictably cause neutropenia, depending on dose and the individual characteristics of the drug (like class and target cell) by affecting production.

**Neutropenic and cytotoxic drugs**

Neutropenia and fever is major dose-limiting effect of many cytotoxic drugs. The incidence of neutropenic fever is directly related to depth and duration of the neutropenia. This depends on the intensity of regimens used and patient- and disease-related factors. This may be and is currently used to classify patients in risk groups. Incidence rates vary enormously, depending on patient groups described, and is generally much higher in patients treated for acute leukemias or stem cell transplantation. In nonleukemic patients leucopenia (World Health Organisation (WHO) grade 4) varies between 2 and 28%, febrile neutropenia up to 10 to 57%,
infections (WHO grades 3 or 4) up to 16% but death in febrile neutropenia is less than 7%. In chemo-naive patients these incidence rates are lower. Neutropenic fever generally results in hospitalization, with its related economic burden. Therefore, there should be a strong urge to prevent these costs.

**Risk of serious complications**

The initial clinical evaluation focuses on assessing the risk of serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, IV antibiotics, and prolonged hospitalization.

Low-risk patients are defined as those who are expected to be neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days and those with no comorbidities or evidence of significant hepatic or renal dysfunction. This group of patients has been well studied in randomized trials and has been shown to be at low risk for serious complications. Most patients receiving chemotherapy for solid tumors are considered to be low-risk for complications requiring hospitalization or prolonging hospitalization.

High-risk patients as those who are expected to be neutropenic (ANC <500 cells/microL) for >7 days. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high-risk, regardless of the duration of neutropenia. Some experts have defined high-risk patients as those expected to have profound neutropenia (ANC ≤100 cells/microL) for >7 days based on experience that such patients are the most likely to have life-threatening complications. However, formal studies to clearly differentiate between patients with an ANC <500 cells/microL and ≤100 cells/microL are lacking.

**Management of neutropenia**

Although not all patients with neutropenia develop neutropenic fever, neutropenia is a significant risk factor for infections. Disruption of defense mechanisms may increase the likelihood for infections, as is the duration and depth of the neutropenia. Several factors have been identified, which can be influenced and lower the likelihood of developing infection.
Less chemotherapy-dose reduction

As cytotoxic drugs, and sometimes radiation or the combination of both are the main causative factors for neutropenia, dose reduction may prevent neutropenia. However, for many drugs there is a significant dose-response relationship. So, decreasing doses may decrease efficacy, which has been demonstrated in several malignancies like breast cancer and Hodgkin’s disease. This makes dose reduction in patients with a curative treatment less attractive. In these patients growth factor support should be considered. In case of palliative treatment indications, one should clearly consider the option of dose reduction and whether the palliative potential can be reached with this dose reduction.

Growth factors; primary prophylaxis

Primary prophylaxis refers to the use of granulocyte CSFs during the first cycle of myelosuppressive chemotherapy with the goal of preventing neutropenic complications. Primary prophylaxis may be used to decrease the incidence of neutropenic fever and the need for hospitalization. Primary prophylaxis may also be used to maintain dose-dense or dose-intense chemotherapy strategies that have survival benefits or if reductions in chemotherapy dose-intensity or dose-density are known to be associated with a poorer prognosis.

Since the introduction of the hematopoietic growth factors granulocyte macrophage colony stimulating factor (GM-CSF) (Sargramostim), granulocyte colony stimulating factor (G-CSF)(Lenograstim and Filgrastim) and pegylated Filgrastim many trials have been performed to assess the value of these drugs in preventing neutropenia and neutropenic fever and, also, in enabling dose adherence. It is now well established that growth factors can prevent up to 50% of occurrences of neutropenic fever, however, without clear benefits in survival or response. This translates in an overtreatment of at least 50% of patients, without benefit and decreasing costs-benefit. If the likelihood of developing neutropenic fever increases over 40% growth factor support may be considered. This also may apply to situations where dose reduction (necessary for neutropenic fever in previous cycles) is deemed detrimental for treatment outcome. The later procedure is called secondary prophylaxis. Several data suggest that the likelihood of neutropenic fever is highest
during the first cycles of chemotherapy. Primary prophylaxis may also be considered in patients with reduced marrow reserve, human immunodeficiency virus infection, active infections, or reduced performance status. In patients with a high-risk for neutropenic fever like those with bone marrow transplantation growth factor support can be helpful. Although not recommended in the European Society for Medical Oncology (ESMO) guidelines, growth factor support may be used in acute myeloid leukemia (AML) trials not to reduce infections but to increase efficacy of chemotherapy.

Evidence from multiple randomized trials and meta-analyses supports the benefit of primary prophylaxis in reducing the frequency of hospitalization for antibiotic therapy, documented infection, and rates of neutropenic fever in adults. Guidelines specifically recommend against the routine administration of granulocyte CSFs for primary prophylaxis in previously untreated adult patients receiving chemotherapy regimens with a low probability (<10 percent) of causing fever during anticipated periods of neutropenia. However, primary prophylaxis may be appropriate in a number of clinical settings in which the estimated risk of neutropenic fever is between 10 and 20 percent.

Growth factors; secondary prophylaxis

Patients with neutropenic fever have an increased risk to develop the same problem during subsequent therapy. If dose reduction is detrimental for the patient and other etiological factors for neutropenia have been excluded or not improved (e.g. bone marrow infiltration) secondary prophylaxis may be considered. In these patients the cost-benefit balance is in favor for growth factor support. Secondary prophylaxis refers to the administration of a granulocyte CSF in subsequent chemotherapy cycles after neutropenic fever has occurred in a prior cycle. A prior episode of fever during neutropenia is a risk factor for developing fever during neutropenia in later cycles, with recurrences noted in 50 to 60 percent of patients. Secondary prophylaxis with CSFs reduces this risk by approximately one-half. The concept of secondary prophylaxis also includes the use of a granulocyte CSF to speed recovery from neutropenia due to a previous cycle of chemotherapy, thus preventing delay in the administration of a subsequent chemotherapy cycle. The goal of secondary
prophylaxis is to maintain chemotherapy dose intensity while avoiding dose reduction. However, dose reduction after an episode of severe neutropenia should be considered the primary therapeutic option, unless chemotherapy is being administered for the treatment of curable tumors (eg, lymphoma, germ cell cancer, early stage breast cancer). In theory, the survival benefit associated with potentially curative chemotherapy is preserved as long as doses are not reduced below a critical level. However, no published regimen has ever shown improved disease-free or overall survival when secondary prophylaxis was instituted and the dose of chemotherapy maintained in any setting.

ASCO and EORTC guidelines suggest that secondary prophylaxis with granulocyte CSFs be limited to patients who experience a neutropenic complication (ie, fever, treatment delay) from a prior cycle of chemotherapy (for which primary prophylaxis was not received) if reduced dose intensity might compromise treatment outcome.

Antibiotics

Prophylactic antibiotic therapy to prevent infections in potentially neutropenic patients has a broad application, especially in the high-dose regimens in hematological malignancies. This approach shows a debatable benefit. Arguments against prophylactic antibiotic use include but are not limited to the potential emergence of resistance against antibiotics. However, in two recently published randomized trials, levofloxacin had not only a significant impact on the reduction of fever, probable infection and hospitalization in low-risk patients with lymphoma and solid tumors but also in high-risk patients with profound and prolonged neutropenia.

Application of growth factors

Originally two growth factors have been developed: G-CSF and GM-CSF. Currently almost all treatments are with G-CSF, largely because of a relatively lack of side effects compared to GM-CSF. Apart from G-CSF (Lenograstim or Filgrastim) which both have to be administered daily, currently also a once per cycle growth factor is available (peg-filgrastim). Generally the use of 5 lg/kg/day of G-CSF subcutaneously 24–72 h after the last day of chemotherapy until sufficient/stable absolute neutrophil
count (ANC) recovery is recommended. It is not necessary to treat patients till they achieve a target ANC of >10 • 109/l.

References


UPDATE MANAGEMENT OF MULTIPLE MIELOMA

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Introduction
Multiple myeloma (MM) is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This clone of plasma cells proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. The diagnosis of MM is often suspected because of one (or more) of the following clinical presentations:

• Bone pain with lytic lesions discovered on routine skeletal films
• An increased total serum protein concentration and/or the presence of a monoclonal protein in the urine or serum
• Systemic signs or symptoms suggestive of malignancy, such as unexplained anemia
• Hypercalcemia, which is either symptomatic or discovered incidentally
• Acute renal failure with a bland urinalysis or rarely the nephrotic syndrome due to concurrent primary amyloidosis.

It is important to distinguish MM both from other causes of the clinical presentations above and from other plasma cell dyscrasias for the purposes of prognosis and treatment. It is also important to evaluate patients suspected of having MM in a timely fashion since a major delay in diagnosis has been associated with a negative impact on the disease course. Multiple myeloma (MM) accounts for approximately one percent of all cancers and slightly more than 10 percent of hematologic malignancies in the United States (US). The annual incidence in the US is approximately 4 to 5 per 100,000. A similar incidence has been reported in the South Thames area of the United Kingdom and in Europe in general.

Diagnosis
The Mayo Clinic and the International Myeloma Working Group criteria for the diagnosis of symptomatic MM emphasize the importance of
end organ damage in making the diagnosis. The following three criteria must be met for the diagnosis of symptomatic MM:

- Presence of an M-protein in serum and/or urine.
- Presence of 10 percent or more clonal bone marrow plasma cells.
- Presence of related organ or tissue impairment (often recalled by the acronym CRAB) which can include increased plasma calcium level, renal insufficiency, anemia, and lytic bone lesions typically detected by radiographic survey.

**Staging**

Once the diagnosis of myeloma is made, patients undergo an initial evaluation to determine the disease stage (ie, the tumor burden). Two main staging systems exist: the International staging system (ISS) and the Durie-Salmon staging system. Of these, the ISS has become the preferred staging system because of its simplicity and lack of subjectivity. Other prognostic studies, such as bone marrow cytogenetics and studies of chromosomal translocations are more frequently used to determine the preferred treatment approach. An International Staging System (ISS) was developed based on 10,750 previously untreated patients with myeloma from over 17 institutions worldwide. It incorporates data on the levels of serum beta-2 microglobulin (B2M) and serum albumin to divide disease burden into three stages with prognostic significance:

- Stage I — B2M <3.5 mg/L and serum albumin ≥3.5 g/dL
- Stage II — neither stage I nor stage III
- Stage III — B2M ≥5.5 mg/L

Median overall survival for patients with ISS stages I, II, and III were 62, 44, and 29 months, respectively.

The Durie-Salmon clinical staging system incorporates several factors correlating with tumor cell mass. Using this method, stage is determined based upon a subjective measure of tumor cell density in the bone marrow along with measures of end organ damage (renal insufficiency, anemia, hypercalcemia, lytic bone lesions) and immunoglobulin burden. While it is a standardized system for the staging of multiple myeloma, the Durie-Salmon staging system has a number of shortcomings relating to its ability to predict prognosis and survival. As an example, this system incorporates the observer-dependent quantitation of
lytic lesions on skeletal survey. Including subjective measures decreases its precision.

**Prognostic**

Patient and tumor specific factors that best predict the survival of patients with myeloma include those incorporated into the staging systems described above and certain cytogenetic studies.

**Patient factors**

The clinical outcome for patients with myeloma depends upon a complex interaction between biologic features of the plasma cell clone and patient specific factors such as age, performance status, and comorbidities. Patients with comorbidities that limit their ability to withstand treatment will have a poor outcome even if they have a myeloma with features commonly associated with a better prognosis. While much of the research evaluating prognosis in myeloma has focused on the biologic properties of the malignant clone, large case series have identified numerous prognostic factors in patients with myeloma, some of which are patient dependent factors.

**Disease factors**

Cytogenetic abnormalities are powerful prognostic factors in myeloma. A combination of conventional cytogenetics and interphase fluorescence in situ hybridization (FISH) is currently used to stratify tumors into high and standard risk disease. FISH for detection of t(11;14), t(6;14), t(4;14), t(14;16), t(14;20), del17p13, and trisomies of odd numbered chromosomes and conventional cytogenetics (karyotyping) for detection of del 13, monosomy 13, or hypodiploidy.

*Beta-2 microglobulin.* The serum beta-2 microglobulin level is one of the prognostic factors incorporated into the International staging system. The serum beta-2 microglobulin level is elevated (ie, >2.7 mg/L) in 75 percent of patients at the time of diagnosis. Patients with high values have inferior survival.

*Bone marrow plasma cell immunophenotype.* The malignant plasma cells in multiple myeloma generally express cytoplasmic immunoglobulin, CD38, CD56 (neural cell adhesion molecule), and CD138.
Monoclonal protein. The clinical course of myeloma may be determined in part by the type of monoclonal protein produced.

Circulating plasma cells. Monoclonal plasma cells can be detected using a slide-based immunofluorescence assay in the peripheral blood of 100 percent of patients with plasma cell leukemia, 80 percent of those with active multiple myeloma, and in more than 90 percent of those with relapsed or refractory myeloma.

Serum free light chain ratio. The serum kappa/lambda free light chain (FLC) assay is a sensitive method for the detection of excess free light chains and an abnormal kappa/lambda FLC ratio is used as a surrogate marker for clonal expansion.

Plasma cell labeling index. An elevated value (ie, ≥1 percent) in a patient with apparent MGUS or SMM may suggest early disease progression and the need for careful follow up. A normal value is less helpful in differentiating MM from MGUS, since it is seen in 35 percent of patients with overt MM requiring therapy. An elevated value in patients with apparently stable, plateau phase MM is an adverse parameter that may predict a short time to disease progression and death.

Management

In the decades of the ‘80s and ‘90s, high-dose melphalan with stem cell rescue was one of the few techniques/treatments available to reduce myeloma tumor burden and achieve better outcomes. With the introduction of thalidomide for myeloma treatment in 1997, the options suddenly changed. Complete responses could be achieved with a simple oral agent. Additional new agents followed in rapid succession: first VELCADE®, then Revlimid®, and now carfilzomib and pomalidomide, which are poised for early approval by the FDA. Other agents such as elotuzimab, vorinostat, panobinostat, and others are showing promising results. Bortezomib is a proteasome inhibitor, the mechanism of action of thalidomide and lenalidomide is unclear, but they are considered immunomodulatory agents and may require cereblon (the putative primary teratogenic target for thalidomide) expression for their anti-myeloma activity. More recently carfilzomib (a new proteasome inhibitor) and pomalidomide have been approved for the treatment of multiple myeloma. There is no single answer to the question of “the best” treatment options available in 2011.
Fortunately, there are numerous regimens that produce very deep responses (more than 90% reduction of M-component [VGPR]), durable responses (remissions lasting ≥2 years), and improved overall survival. The best choice for each patient depends upon individual factors such as age, stage, genetic features, kidney status, and of course personal preference. It has become an open question whether immediate auto transplant as a part of first treatment is required or whether it can be offered as an option at first relapse, for example. It is important that myeloma patients be aware of the need for careful discussions with their physicians.

There is an ongoing “cure versus control” debate on whether we should treat myeloma with an aggressive multi-drug strategy targeting complete response (CR) or a sequential disease control approach that emphasizes quality of life as well as OS [2,86]. Based on recent data, high-risk patients require a CR for long-term OS and hence clearly need an aggressive strategy. On the other hand, standard-risk patients have similar OS regardless of whether CR is achieved or not and therefore have the option of pursuing either an aggressive or a sequential approach.

**Options for initial treatment in patients eligible for ASCT**

In standard-risk patients, Rd or VCD can be used as initial therapy for 4 months, followed by stem cell harvest and ASCT. In patients who are tolerating therapy and responding well, it is equally reasonable to continue initial therapy after stem cell collection, reserving ASCT for first relapse. With such a strategy, therapy is usually stopped after 12 to 18 months. In general, Rd as initial therapy in standard-risk patients with trisomies, and VCD in standard-risk patients who have t(11;14) or t(6;14) translocation. But in intermediate-risk patients, VCD as initial therapy for four cycles followed by ASCT and then maintenance with a bortezomib-based regimen for at least 2 years. In high-risk patients, VRd as initial therapy for four cycles followed by ASCT and then long-term maintenance with a bortezomib-based regimen.

In patients presenting with acute renal failure suspected to be secondary to light-chain cast nephropathy, VCD or VTD as initial therapy in conjunction with plasma exchange. Plasma exchange is continued daily until the serum free light chain levels are less than 50 mg/dL and then repeated as needed till chemotherapy is fully effective. Patients with
plasma cell leukemia or multiple extramedullary plasmacytomas, VDT-PACE as initial therapy followed by ASCT and then maintenance with a bortezomib-based regimen. Once weekly subcutaneous bortezomib is preferred in most patients for initial therapy, unless there is felt to be an urgent need for rapid disease control. Dexamethasone 40 mg once a week (low-dose dexamethasone) is preferred preferred in most patients for initial therapy, unless there is felt to be an urgent need for rapid disease control.

Options for initial treatment in patients not eligible for ASCT

In standard-risk patients, as in the transplant eligible population, Rd or VCD can be used as initial therapy. In general, Rd as initial therapy in standard-risk patients with trisomies, and VCD in standard-risk patients who have t(11;14) or t(6;14) translocation. The duration of therapy when using Rd is until disease progression, whereas VCD is given for approximately 12 months. Dexamethasone dose is reduced as much as possible after the first 4-6 months, and possibly discontinued after the first year. For frail patients, dexamethasone may be started at 20 mg once a week. For intermediate-risk patients, VCD as initial therapy for approximately one year followed if possible by a lower intensity (one dose every 2 weeks) maintenance schedule of bortezomib for 2 years. In high-risk patients, VRd as initial therapy for approximately 1 year followed by a lower intensity maintenance schedule of bortezomib.

References


MULTIPLE MYELOMA

The role of Bortezomib in the management of multiple myeloma

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Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cell in the bone marrow, in most cases associated with monoclonal protein in the blood and/or urine. It is the second most common hematologic malignancy in the adults, accounts for 1% of all cancers and approximately 10% of all hematologic malignancies, with incidence approximately 4/100,000/year. MM is disease of elderly with the median age at diagnosis is 65 years.

MM is probably one of the hematologic malignancies in which major progress (from bench to bedside – from biology to therapeutics) has occurred in over the last 15 years. Biology has moved from protein analysis into genomics, while therapeutics has moved from 1 active agent (melphalan) to almost uncountable potentially active drug combination, immunomodulators (thalidomide and lenalidomide) and proteasome inhibitor (bortezomib) as the benchmark. In pathogenesis of MM, there are 2 key players: (1) the genetic lesions intrinsic to the malignant clone; and (2) the interaction between myelomatous plasma cells (PCs) and their microenvironment. Almost all patients with myeloma evolve from asymptomatic pre-malignant stage termed monoclonal gammopathy of undetermined significance (MGUS) to an intermediate asymptomatic but more advanced premalignant state referred as smouldering multiple myeloma (SMM), to the active symptomatic malignant disease termed as multiple myeloma (MM). MGUS is present in over 3% of population above the age of 50, and progresses to myeloma at rate of 1% per year.

MGUS and SMM are asymptomatic. The main symptoms and signs of MM are related to end-organ damages that can be related to the underlying plasma cell disorders: hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB). The diagnostic criteria of plasma cell
disorders were redefined in 2003. Diagnosis of MM need clonal bone marrow plasma cells ≥ 10% or biopsy proven plasmacytoma with evidence of end-organ damages (CRAB). In the absence of end-organ damage, clonal bone marrow plasma cells should be ≥ 60%. When MM is suspected clinically, patients should be tested for the presence of M proteins using a combination of test that should include SPE (serum protein electrophoresis), serum immunofixation, and serum free light chain assay. Karyotyping and FISH are recommended to detect hypodiploidy, deletion 13, t(11;14), t(4;14), t(14;16), t(6;14, t(14;20), trisomy, and deletion 17p. These data are need for evaluation of Risk Stratification of Myeloma. Prognosis in myeloma depends on host factors (age, performance status, comorbidities), stage, disease aggressiveness, and response to therapy. Staging of myeloma using Durie – Salmon Staging System (DSS) was replaced by the International Staging System (ISS). ISS is more simple (only use β-2 microglobulin and total protein) with better prognostic prediction. DSS and ISS provides prognostic infromation but is not helpful in making therapeutic strategy. Risk Stratification of Myeloma using Mayo strafication for myeloma and risk-adapted therapy classification (mSMART) is useful for both counseling and therapeutic decission making. MM is stratified into standard, intermediate, and high-risk disease.

Major progress in the treatment of MM has been achieved in last 15 years. With the use of combined melphalan and prednisone nearly 50 years ago, median survival of patients with MM was extended to 2 to 3 years. In the 1980s, high-dose melphalan followed by BM transplantation and with peripheral blood stem-cell rescue in 1990s further increased patient median survival to 3 to 4 years. Since 1998, MM has represented a new paradigm in drug development because of the remarkable therapeutic efficacy of targeted therapy. In particular, the observation that proteasome inhibitor bortezomib and immunomodulatory drugs (ImiDs) - thalidomide and lenalidomide, target the MM cells in the BM microenvironment, has rapidly translated from bench to bedside and six new US FDA approved treatments in the past 7 years, with a doubling of patient survival from 3 to 4 to 7 to 8 years as a direct results.

The clinical application of 3 therapeutic strategies has profoundly altered the natural history of MM: melphalan and prednison in the 1950s and 1960s, ASCT pioneered in the 1980s, and the proteasome inhibitor
(PI) bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide in the late 1990s to early 2000s, together in ancillary care of MM-related bone disease have resulted in step-wise overall survival (OS) from 1 to 2 years to the current 7 to 8 years and in a better quality of life. Immunomodulatory drugs (IMiDs) target the MM cell in the BM microenvironment, modulate adhesion molecules of myeloma cells and their surrounding stroma, modulate cytokines, affect natural killer cell, and have an anti-angiogenic properties. Thalidomide is the first of IMiDs, it has combined with a variety of agents including dexamethasone, cyclophosphamide, etoposide, and liposomal doxorubicin. Despite high response rates, responses are transient and can be associated with significant toxicities. Lenalidomide is a potent analogue of thalidomide, more potent than thalidomide in mediating direct cytokine-related and immunomodulatory effects against human multiple myeloma cell lines. In 2006, the combination of lenalidomide and dexamethasone was approved by FDA as therapy for relapsed and refractory MM. The FFP (freedom from progression) and OS (overall survival) is significantly increase. The side effects are neutropenia and veno-ous thromboembolism, therefore the use of antithrombotic prophylaxis is recommended. Bortezomib (Velcade – Johnson & Johnson) is the first proteasome inhibitor approved by US FDA. Bortezomib works in the ubiquitine-proteasome pathway of cellular protein homeostasis by blocking the action of the 26S proteasome, leads to cell apoptosis. Bortezomib combined with other agents for previosuly untreated or refractory/relapase MM: VMP (velcade, melphalan and prednisone), VT (velcade, thalidomide), VCP (velcade, cyclophosphamide, prednisone), VCD (velcade, cyclophosphamide, dexamethasone), VRD (velcade, lenalidomide, dexamethasone), VBP (velcade, bendamustine, prednisone), PAD (bortezomib,doxorubicin, dexamethasone). These combinations give a varied effectivitiness in MM preferred for transplant candidates and for non-transplant candidates.

Patients with MGUS and smoldering MM, do not need primary therapy. Active (symptomatic) MM are initially treated with primary therapy and, in selected patients, followed by high-dose chemotherapy with autologous stem cell support. One of the first step in evaluating patients with advanced MM is to determine wheteher they are candidates for high-dose therapy and transplant, based on age and comorbidities. Stem cell
toxins, such as nitrosurea or alkylating agent may compromised stem cell reserve, and regimens of these agents (notably melphalan) should be avoided in who are potential candidates for SCT.

**Preferred primary therapy regimens for transplant candidates**

**Bortezomib / dexamethasone (Veldex) regimen**: the IFM trial comparing VAD (vincristine, adriamycin, dexamethasone) with bortezomib/dexamethasone (Veldex). The overall response rate (78.5% vs 62.6%), CR rate (14.8% vs 6.4%). Based on this data NCCN listed bortezomib-dexamethasone regimen as a category 1 primary therapy option for transplant-eligible patients with MM.

**Bortezomib/doxorubicin/dexamethasone (PAD) regimen**: updated results from HOVON-65/GMMG-HD4, comparing PAD to VAD regimen, give a superior response rate (CR + near CR: 31% vs 15%). Based on this data NCCN listed PAD regimen as a category 1 primary therapy option for transplant-eligible patients with MM.

**Bortezomib/thalidomide/dexamethasone (VTD) regimen**: The GIMEMA Italian Multiple Myeloma Network reported results of investigating VTD regimen vs thalidomide/dexamethasone (TD). The addition of bortezomib significantly improved ORR (CR/nearCR: 31% vs 11%). The results of Spanish Myeloma Group also demonstrated a significantly higher CR rate with VTD (35% vs 14%). Based on this data NCCN listed VTD regimen as a category 1 primary therapy option for transplant-eligible patients with MM.

**Cyclophosphamide/bortezomib/dexamethasone (VCD) regimen**: trial by Rieder et al showed overall response rate (ORR 88%), and EVOLUTION study give result with ORR of 75%. Based on this data NCCN listed VCD regimen as a category 2A primary therapy option for transplant-eligible patients with MM.

**Bortezomib/lenalidomide/dexamethasone (VRD) regimen**: Phase I/II study have shown VRD is active and well tolerated in newly diagnosed MM, with CR/near CR rate was 52%. In IFM 2008 trial. OR rate was 97%, with CR
rate was 16%. Based on this data NCCN listed VRD regimen as a category 2A primary therapy option for transplant-eligible patients with MM.

**Preferred Primary Therapy Regimens for Non-transplant Candidates**

**Melphalan/prednison/thalidomide (MPT) regimen:** Melphalan and prednison (MP) has been a standard treatment of MM since 1960s. The IFM01-01 study compared MP with MPT regimen, after follow-up time of 47.5 months, median OS was significantly prolonged in MPT group (44 months vs 29.1 months). Study by HOVON group in 33 newly diagnosed elderly patient of MM, significantly higher response rates were seen with MPT-treated patients compared to MP. A meta-analysis has demonstrated that in in previously transplant-ineligible, elderly patients with MM, MPT results in significantly improved response rate and PF with a trend towards improvement in OS compared with MP alone. Based on this data NCCN listed MPT regimen as a category 1 primary therapy option for transplant-ineligible patients with MM.

**Melphalan/prednison/lenalidomid (MPL) regimen:** MM-015 trial compared MPL induction to MP. MPL regimen had a higher speed of response, ORR and response quality. The MPL regimen is category 1 primary treatment option for patients ineligible for transplant in the NCCN Guidelines for Multiple Myeloma.

**Melphalan/prednisone/bortezomib (MPB) regimen:** VISTA trial comparing 383 patients on MP and 344 patients on MPB, after median follow up of 60.1 months, showed a 31% reduced risk of death, median duration of OS (56.4 months vs 43.1 months), with 5-year OS rates of 46.0% with MPB vs 34.4% with MP. Based on the VISTA trial results, the MPB regimen is now a NCCN category 1 primary treatment option for transplant-ineligible patients with MM.

**Bortezomib/dexamethasone regimen:** UPFRONT trial compared safety and efficacy of three highly active bortezomib-based regimens. The OR rate of bortezomib/dexamethasone was 73%, 80% of bortezomib/thalidomide/dexamethasone, and 69% of MPB. The NCCN Multiple Myeloma Panel has included bortezomib and dexamethasone as
category 2A primary therapy for patients with MM who are ineligible for transplant.

**Disadvantages of bortezomib:** significance challenges remain for bortezomib as anticancer drugs, such as (1) severe side effects; (2) drug resistance; (3) reduction of bortezomib’s efficacy due to its interactions with some natural compounds. The most frequent side effects (incidence > 30%) associated with bortezomib include asthenic conditions, gastrointestinal symptoms (nausea, vomiting, diarrhea), hematological toxicity (thrombocytopenia and anemia), and peripheral neuropathy (hypoaesthesia and paresthesia). About 35% of MM patients are sensitive to bortezomib. Bortezomib resistance which appears to be associated with proteasome subunit β5 mutations. Green tea polyphenols, dietary flavonoids and ascorbic acid inhibit the anticancer effects of bortezomib.

Based on the results of many phase II and phase III trials for eligible or ineligible MM patients, bortezomib containing regimens showed efficacy. Proteasome inhibitor has assumed a central role in the management of MM due to the effectiveness of the treatment strategy, a manageable safety profile, and the ability to combine proteasome inhibitors with other chemotherapeutic agents.
PENDEKATAN TERHADAP PENDERITA ANEMIA

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Abstrak

Anemia merupakan masalah kesehatan yang sering ditemui di masyarakat. Konsekuensi klinis yang ditimbulkan dapat melibatkan gangguan fungsi organ yang penting seperti kardiovaskuler, paru-paru, gastrointestinal, sistem saraf, serta perubahan pada kulit dan mukosa. Dampaknya pada kesehatan fisik cukup besar, secara tidak langsung anemia juga mempengaruhi kesejahteraan sosial dan ekonomi akibat debilitas kronik yang ditimbulkannya.

Anemia secara fungsional didefinisikan sebagai penurunan jumlah massa eritrosit (red cell mass) sehingga tidak dapat memenuhi fungsinya untuk membawa oksigen ke jaringan perifer (penurunan oxygen carrying capacity). Secara praktis anemia ditunjukkan secara klinis maupun laboratorik. Parameter laboratorium yang umum digunakan adalah penurunan kadar hemoglobin, hematokrit atau hitung eritrosit. Namun pada beberapa kondisi klinis, ketiga parameter ini tidak menunjukkan kondisi penurunan eritrosit yang sebenarnya seperti kondisi dehidrasi, kehamilan, atau perdarahan akut. Selain itu kadar hemoglobin dan eritrosit juga sangat bervariasi, tergantung dari usia, jenis kelamin ataupun ketinggian tempat tinggal.

Hal penting yang harus diperhatikan dalam pendekatan diagnosis terhadap penderita anemia adalah penyakit yang mendasari munculnya anemia. Karena anemia adalah suatu sindroma dan bukan merupakan satu kesatuan penyakit. Penatalaksanaan yang tepat dan adekuat dapat diberikan jika kita mengetahui kondisi penyakit yang mendasari terjadinya anemia tersebut.

Terdapat beberapa macam pendekatan diagnosis anemia, yaitu pendekatan tradisional dimana pendekatan dengan jalan melakukan
Mekanisme kerja

Fludarabine phosphate adalah analog adenine yang diflurinasi yang relatif resisten terhadap deaminasi dari adenosine deaminase. Fludarabine phosphate (2F-ara-AMP) merupakan prodrug yang larut dalam air yang dengan cepat mengalami deforforilasi menjadi 2-fluoro-ara-A (2F-ara-A) kemudian defosforilasi secara intraseluler oleh deoxycytidine kinase menjadi triphosphate 2-fluoro-ara-ATP (2F-ara-ATP) aktif. Aktifitas anti tumor fludarabine ini ditentukan oleh bahan aktif ini untuk menghambat sintesis DNA dengan menghambat ribonucleotide reductase, DNA polymerase α, dan ε, DNA primase dan DNA ligase. Selain itu fludarabine juga menghambat sebagian dari RNA polymerase II dan pada akhirnya akan hambatan pembentukan protein. Efek obat ini terhadap DNA, RNA dan sintesis protein akan menyebabkan hambatan pertumbuhan sel, terutama yang paling utama adalah menghambat DNA.

Penggunaan Fludarabine pada beberapa kondisi klinik

Penggunaan secara luas dari fludarabine adalah pada kasus chronic lymphocytic leukemia (CLL). Complete dan partial respon rate (CR + PR) pada kasus CLL yang sudah mendapat terapi adalah menjadi 50% dan CR + PR sebanyak 70% - 85% pada kasus-kasus CLL yang belum pernah mendapat terapi sebelumnya dengan atau tanpa prednisone. Percobaan-percobaan klinis selanjutnya juga menunjukkan hasil yang baik pada kasus-kasus Waldenstrom’s macroglobulinemia. Studi klinis fase I dan II dari fludarabine menunjukkan bahwa obat ini juga bermanfaat untuk pasien dengan indolent lymphoma. Sekitar 60% pasien dengan follicular lymphoma memberikan respon terhadap fludarabine sebagai terapi

Fludarabine pada kasus CLL

CLL merupakan penyakit leukemia yang paling sering terjadi pada orang dewasa dengan insiden sekitar 2 – 4 kasus per 100.000 penduduk di Negara-negara barat dan insidennya meningkat menjadi lebih dari 20 orang per 100.000 penduduk pada umur di atas 70 tahun. Penyakit ini secara umum bersifat indolen, dengan remisi dan kekambuhan yang berulang dengan penurunan kualitas hidup. Beberapa prognostic faktor telah diidentifikasi seperti stadium dari penyakit, kelainan kromosom (delesi 17p, 13q, 11q atau trisomy 12), satus mutasi dari immunoglobulin heavy-chain variable region (IgVH) dan ekspresi berlebihan dari CD38 dan atau ζ-chain-associated protein kinase 70 (ZAP-70).

CLL masih merupakan penyakit yang incurable dengan kemoterapi konvensional oleh karena itu diperlukan pengobatan yang lebih baru. Beberapa terapi yang dipakai saat ini adalah alkylating agents (dengan atau tanpa steroid) dan purine nucleoside analog yang digunakan secara tunggal atau kombinasi. Penelitian-penelitian menunjukkan Fludarabine memiliki efek yang lebih superior untuk terapi CLL dibandingkan dengan alkylating agent-based chemotherapy dan kombinasi fludarabine dan cyclophosphamide (FC) memberikan efek complete remission (CR) dan duration response (DR) lebih baik dibandingkan dengan fludarabine tunggal. Rituximab sebagai monoclonal antibody CD 20 apabila dikombinasikan dengan FC akan untuk terapi CLL meyebabkan CR dan DR menjadi lebih baik.
DAFTAR PUSTAKA


RECOMBINANT FACTOR VIIa DALAM MANAJEMEN KELAINAN PERDARAHAN YANG JARANG DIJUMPAI

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Kemajuan dalam pengertian prinsip dasar koagulasi telah berkembang sampai saat ini. Teori koagulasi semula dikenal sebagai teori waterfall atau teori kaskade, telah berkembang menjadi teori koagulasi berbasis sel dan terakhir teori hemostasis berbasis partikel. Faktor VII adalah faktor koagulasi yang sangat penting dalam extrinsic pathway. Kompleks faktor VIIa dengan TF (tissue factor) dapat melakukan “bypass” sehingga mengaktifkan common coagulation cascade yang menghasilkan faktor Xa. Ini berarti faktor Xa dapat terjadi tanpa memerlukan faktor VIII atau faktor IX. Semua proses ini terjadi di atas permukaan thrombosit yang mengalami aktivasi (activated platelet).

Recombinant Factor VIIa semula dipakai untuk penderita hemophilia A dan B yang disertai pembentukan antibodi yang merupakan inhibitor terhadap faktor VIII atau faktor IX sehingga penderita resisten terhadap terapi faktor VIII dan faktor IX. Kemudian rFVIIa ternyata diindikasikan juga pada acquired hemophilia, congenital factor VII deficiency dan Glanzmann thromboasthenia. Pada perkembangan selanjutnya rFVIIa dipakai untuk berbagai perdarahan terutama akibat trauma. Penggunaan rFVIIa yang sudah mendapat persetujuan resmi (on-label) adalah untuk congenital hemophilia yang disertai inhibitor, acquired hemophilia A, congenital FVII deficiency dan thrombosthenia Glanzmann. Berbagai laporan dipublikasikan mengenai penggunaan rFVIIa dalam mengatasi perdarahan akibat trauma, perdarahan kritis di ICU, dan berbagai perdarahan lainnya, tetapi penggunaan ini masih terbatas, belum mendapat persetujuan resmi (off-label).

Acquired hemophilia A (AHA), adalah penyakit yang jarang dijumpai tetapi secara potensial dapat menimbulkan perdarahan yang mengancam jiwa. AHA disebabkan karena timbulnya auto-antibody terhadap faktor VIII (factor VIII inhibitor). Sekitar 50% AHA bersifat idiopatik, tanpa penyakit
dasar, sedangkan sebagian dijumpai penyakit dasar yaitu kehamilan, penyakit autoimun, dan keganasan. Perbedaan AHA dengan hemophilia kongenital adalah pada antibodi yang timbul, pada AHA yang timbul adalah autoantibodi, sedangkan pada hemophilia kongenital adalah aloantibodi. AHA dapat mengenai wanita maupun laki-laki dengan porsi yang sama. Gejala perdarahan pada AHA berupa perdarahan jaringan lunak, perdarahan otot, perdarahan urogenital atau gastrointestinal. Hemarthrosis jarang dijumpai. Terapi perdarahan pada AHA dilakukan sesuai dengan tatalaksana perdarahan pada umumnya, hindari tindakan intervensi dan obati penyakit dasar. Terapi perdarahan akut pada AHA adalah pemberian rFVIIa, tetapi dapat juga diberikan aPCC. Terapi alternatif adalah DDAV. Terapi jangka panjang untuk menghentikan produksi antibodi adalah dengan steroid, tetapi disertai efek samping yang banyak. Yang sekarang menjanjikan adalah pemberian rituximab. Summer at al. Meneliti 204 episode perdarahan pada 139 AHA, menunjukkan overall success rate 88%, 95% jika dipakai sebagai first-line dan 80% jika dipakai sebagai second-line treatment. FENOC study menunjukkan success rate untuk rFVIIa sebesar 78%. Dosis yang direkomendasikan adalah 90 µg/kg diberikan setiap 2-3 jam.

Inherited factor VII deficiency adalah penyakit perdarahan herediter karena mutasi gen yang mengkode sintesis fVII. Penyakit ini sangat jarang dijumpai dan bersifat autosomal resesif. Gejala bervariasi mulai dari perdarahan berat dengan perdarahan intraserebral atau hemarthrosis sampai perdarahan ringan yaitu perdarahan mukokutan. Diagnosis dapat dibuat dengan mengukur kadar FVII, pada penyakit ini kadar FVII dijumpai di bawah 70%. Untuk terapi perdarahan atau pencegahan tindakan invasif dapat diberikan FFP (fresh frozen plasma) tetapi memerlukan volume plasma yang besar serta bahaya penularan penyakit. Dapat juga diberikan FVII concentrates dengan dosis antara 15-50 IU/kg diberikan setiap 6-8 jam. Recombinant FVIIa (NovoSeven) akhir-akhir ini merupakan obat pilihan untuk mengatasi perdarahan atau pencegahan tindakan. Dosis rFVIIa adalah 15-30 µg/kg bolus intravena setiap 4-6 jam sampai perdarahan berhenti.

Thromboasthenia Glanzmann adalah penyakit kelainan perdarahan yang jarang dijumpai dan bersifat herediter. Insidennya dilaporkan 1/1.000.000/tahun. Penyakit ini disebabkan oleh karena defek pada GPIIb
atau GPIIIa sehingga terjadi kehilangan fungsi reseptor GPIIb/GPIIIa yang diperlukan dalam agregasi thrombosit. Pembentukan platelet plug terganggu pada tempat injuri pembuluh darah sehingga terjadilah perdarahan mukokutan dan bruising. Pada pemeriksaan laboratorium dijumpai jumlah thrombosit normal tetapi tes agregasi thrombosit abnormal. Pengobatan dilakukan dengan transfusi trombosit, 15-30% penderita menjadi refrakter terhadap transfusi trombosit karena terbentuk antibodi terhadap GPIIb-IIIa. rFVIIa (novoseven) diberikan untuk mengatasi episode perdarahan pada pencegahan perdarahan pada operasi atau prosedur invasif. Dosis yang direkomendasikan adalah 90 µg/kg dengan injeksi intravena setiap 2 jam. Sedikitnya diberikan 3 dosis untuk menjamin tidak terulangnya perdarahan.

Berbagai publikasi menunjukkan rFVIIa diberikan pada berbagai jenis perdarahan terutama massive bleeding. Belum terdapat konsensus internasional penggunaan rFVIIa pada massive bleeding, masih bersifat lokal dan off-label. Yang dimaksudkan dengan massive bleeding adalah salah satu dari: (1) kehilangan seluruh darah dalam 24 jam (10 unit PRC pada penderita dengan BB 70 kg); (2) kehilangan 50% darah dalam waktu 3 jam; (3) kehilangan darah dengan kecepatan 150 ml/jam; (4) kehilangan darah dengan kecepatan 1,5 ml/kg/menit untuk lebih dari 20 menit. Penanganan perdarahan masif dilakukan dengan: (1) pemberian 8-10 unit PRC; (2) pemberian FFP 10-15 ml/kg (4-6 unit per penderita yang mempunyai berat 70 kg); (3) pemberian cryoprecipitate 1-2 U/10kg; (4) pemberian thrombosit 1 – 2 U/10 kg (10-15 U pada penderita dengan berat badan 70 kg). Pengobatan terakhir sebagai one salvage treatment adalah pemberian rFVIIa. Laporan sementara menunjukkan pemberian rata-rata 1,6 dosis per episode perdarahan. Dilaporkan efektif pada 93,9% kasus.

Karena hasil yang didapat belum berasal dari hasil uji klinik, maka Israeli Multidisciplinary rFVIIa Task Force hanya memeberi sugesti yang tidak bersifat konklusif dalam pemakaian rFVIIa untuk perdarahan masif. Efek samping pemberian rFVIIa, meskipun kecil (< 1 per 1000 dosis standar) tetapi dapat timbul dalam bentuk thrombosis atau DIC.

Pemberian rFVIIa tanpa pembatasan, tanpa evalusai, di luar dari yang sudah mendapat lisensi (licensed) tidak dianjurkan. Pemberian rFVIIa di luar dari yang dilisensikan sampai saat ini hanya dibatasi untuk
keperluan riset dan uji klinis yang ketat yang direncanakan untuk menambah pengetahuan yang sudah ada secara sistematik.
OVERVIEW CHRONIC MYELOID LEUKEMIA

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Pendahuluan


CML merupakan kelainan hematopoietic stem cell yang ditandai dengan translokasi resiprokal antara kromosom 9 dan 22 yang akan menghasilkan kromosom Philadelphia (Ph chromosome). Translokasi t(9;22) akan membentuk BCR-ABL fusion gene dan akan membentuk protein BCR-ABL yang akan mengaktivasi secara tidak normal tirosin kinase. Aktivasi ini merupakan dasar terjadinya dasar dari kelainan hematopoietic progenitor cell yang akan menyebabkan terjadinya proliferasi yang meningkat, diferensiasi yang tergangu dan apotosis yang menurun. CML dibagi menjadi tiga fase yaitu kronik, akselerasi dan krisis blastik. Sebagian besar pasien CML ditemukan dalam fase kronik. Pasien CML fase kronik yang tidak diobati akan menjadi progresif setelah 3 – 5 tahun. Instabilitas genetik disertai dengan perubahan genetik menjadi dasar penyakit ini progresif.

Gejala Klinik

Gejala klinik CML, tergantung pada fase yang kita jumpai pada penyakit tersebut yaitu :

A. Fase kronik terdiri dari :
   1. Gejala hiperkatabolik : berat badan menurun, lemah, anoreksia, berkeriting malam
   2. Splenomegali hampir selalu ada, sering masif
   3. Hepatomegali lebih jarang dan lebih ringan
   4. Gejala gout, gangguan penglihatan, dan priapismus
   5. Anemia pada fase awal sering hanya ringan
6. Kadang – kadang asimtomatik, ditemukan secara kebetulan pada saat check up atau pemeriksaan untuk penyakit lain

B. Fase transformasi akut terdiri atas:

1. Perubahan terjadi pelan-pelan dengan prodromal selama 6 bulan, disebut sebagai fase akselerasi. Timbul keluhan baru: demam, lelah, nyeri tulang (sternum) yang semakin progresif. Respons terhadap kemoterapi menurun, leukositosis meningkat dan trombosit menurun dan akhirnya menjadi gambaran leukemia akut


Kelainan Laboratorium

Pada kasus CML dapat dijumpai kelainan laboratorium berikut:

1. Darah tepi

   a. Leukositosis berat 20.000-50.000 pada permulaan kemudian biasanya lebih dari 100.000/mm³

   b. Apusan darah tepi: menunjukkan spektum lengkap seri granulosit mulai dari mieloblast sampai netrofil, lebih komponen paling menonjol ialah segmen netrofil dan mielosit. Stab, metamielosit, promielosit dan mieloblast juga dijumpai. Sel blast kurang dari 5 %

   c. Anemia mula-mula ringan menjadi progresif pada fase lanjut, bersifat normokromik normositer.

   d. Trombosit bisa meningkat, normal atau menurun. Pada fase awal lebih sering meningkat.

   e. Fosfatase alkali netrofil (neutrophil alkaline phosphatase [NAP] score) selalu rendah

2. Sumsum tulang

Hiperselular dengan sistem granulosit dominan. Gambarannya mirip dengan asupan darah tepi. Menunjukkan spektrum lengkap seri mieloid dengan komponen paling banyak ialah netrofil dan mielosit. Sel blast kurang dari 30%. Megakariosit pada fase kronik nomal atau meningkat.

3. Sitogenetik: dijumpai adanya Philadelphia (Ph1) chromosome pada 95% kasus
4. Vitamin B12 serum dan B12 binding capacity meningkat
5. Pemeriksaan PCR (polymerase chin reaction) dapat mendeteksi adanya chimeric protein bcr-abl pada 99%
6. Vitamin B12 serum dan B12 binding capacity meningkat
7. Kadar asam urat serum meningkat

Tanda-tanda trasformasi akut
Perubahan CML fase kronis ke fase transfromasi akut ditandai oleh:
1. Timbulnya demam, dan anemia yang tidak dapat dijelaskan penyebabnya
2. Respons penurunan leukosit terhadap kemoterapi yang semula baik menjadi tidak adekuat
3. Splenomegali membesar yang sebelumnya sudan mengecil.
4. Blast dalam sumsum tulang > 10%

Diagnosis CML dalam fase akselerasi menurut WHO adalah
1. Blast 10-19 % dari WBC pada darah tepi dan atau dari sel sumsum tulang berinti
2. Basofil darah tepi ≥ 20%
3. Thrombositopenia persiten (<100x10^9/L) yang tidak dihubungkan dengan terapi, atau thrombosistosis (> 1000x10^9/L) yang tidak responsif pada terapi
4. Peningkatan ukuran lien atau WBC yang tidak responsif pada terapi
5. Bukti sitogenetik adanya evaluasi klonal.

Diagnosis CML pada fase krisis blastik menurut WHO adalah:
1. Blast ≥ 20% dari darah putih pada darah perifer atau sel sumsum tulang berinti
2. Poliferasi blast esktramedular
3. Fokus besar atau cluster blast dalam biopsi sumsum tulang

Penatalaksanaan
Selama bertahun-tahun pengobatan CML adalah dengan kemoterapi seperti hydroxiurea dan busulfan. Dengan cara ini gejala penyakit dapat dikontrol tetapi sangat jarang bisa menghilangkan klonal sel yang tidak normal. Selain itu perjalanan alamiah penyakitnya juga tidak

Perkembangan terakhir dengan terapi target terhadap BCL-ABR telah mengubah secara dramatis penatalaksanaan CML dan algoritmenya. Terapi standar CML sekarang ini adalah dengan inhibitor oral BCL-ABR tyrosine kinase. IFN-α sekarang tidak lagi dipakai sebagai terapi awal dan SCT hanya dilakukan pada pasien-pasien yang gagal dengan inhibitor BCL-ABR tyrosine kinase.

CML merupakan contoh penyakit yang memberikan respon yang dramatik terhadap terapi target molekul. Walaupun begitu masih tantangan khususnya pada pasien yang tidak mencapai respon yang optimal atau respon optimal tetapi kambuh lagi. Selain itu banyak pasien yang masih terdeteksi ada sisa penyakit denagn metoda PCR meskipun telah mencapai respon sitogenetik.

**ERA SEBELUM BCR-ABL TYROSINE KINASE**

a. Kemoterapi


b. Interferon Alfa (IFN-α)

Pengenalan IFN-α membuat era baru dalam pengobatan CML. Pengobatan dengan IFN-α member banyak keuntungan dibandingkan dengan busulfan dan hydroxiurea. Mekanisme kerja IFN-α pada pengobatan CML ini tidak sepenuhnya diketahui. IFN-α bekerja pada
sistem imun ayng mempunyai efek sebagai anti leukemik. Selain itu IFN-α memiliki efek antoproliferatif dan anti angiogenesis. IFN-α merupakan obat CML yang pertama dilaporkan bisa memberi respon sitogenetik komplit secara signifikan sampai 20 – 25%. Kombinasi obat ini dengan cytarabine akan menghasilkan respon rate yang lebih baik.

Yang penting adalah dengan pemberian IFN-α bisa mencapai respon sitogenetik yang komplit yang merupakan surrogat marker untuk mencapai survival yang lama. Data terakhir menunjukkan pasien yang mencapai respon sitogenetik secara komplit memeliki angka harapan hidup 10 tahun sebanyak 78%. Studi di atas menunjukkan betapa pentingnya suatu obat bisa mencapai respon sitogenetik dan molekuler. Terjadi hubungan yang kuat antara respon sitogenetik dengan harapan hidup, sehingga goal utama terapi CML adalah respon sitogenetik.

c. Allogenic BMT

Efikasi dari allogenic BMT pada pengobatan CML fase kronik telah dievaluasi melalui beberapa penelitian. Angka harapan hidup tiga sampai lima tahun adalah 30% - 80% dan angkanya lebih tinggi pada tempat yang lebih berpengalaman melakukan BMT. Angka kekambuhan dalam tiga sampai lima tahun kurang dari 20%.

Gale at al, mencoba untuk membandingkan angka harapan hidup 548 pasien CML dari International Bone Marrow Transplant Registry dengan 196 pasien yang mendapat IFN-α atau hydroxiurea. Angka harapan hidup 18 bulan pertama pada pasien yang menjalani BMT lebih rendah dari yang mendapat IFN-α atau hydroxiurea, hal ini mungkin terkait dengan angka mortalitas terkait dengan efek transplantasi. Tetapi angka harapan hidup 7 tahun lebih baik pada BMT dibandingkan dengan yang mendapat IFN-α atau hydroxiurea (56% - 75% dibandingkan 21% - 40%).

Angka kematian dari BMT terkait dengan beberapa efek samping yang sering terjadi. Graft versus host disease (GVHD) merupakan efek yang paling sering dijumpai. GVHD akut terjadi sekitar 8% - 63% dengan angka kematian 2% - 13%. Sedangkan GVHD kronik terjadi antara 4% - 7% dengan angka kematian 8% - 10%. Donor yang tidak sesuai merupakan faktor yang menentukan timbulnya komplikasi GVHD. Interstitial pneumonitis, veno occlusive disesase dan secondary malignancy merupakan efek yang lebih jarang timbulnya.
TERAPI BERBASIS BCR-ABL TYROSINE KINASE

Ditemukannya aktivitas yang tidak normal dari protein Bcr-Abl memiliki peranan yang sangat penting dalam patogenesis CML, sehingga terapi yang berbasis ini akan menjadi sangat berkembang dan memberikan hasil yang lebih baik dari terapi-terapi sebelumnya. Bcr-Abl tyrosine-kinase inhibitor seperti imatinib, dasatinib, nilotinib dan yang lainnya merupakan terapi utama dari CML saat ini dengan memberikan respon hemotologi, sitogenetik dan molekuler yang lebih tinggi.

MONITORING RESPON TERAPI TKI

Monitoring respon terapi TKI pada CML merupakan salah satu kunci keberhasilan strategi. Respon terapi ditentukan dengan mengukur respon hemotologi, sitogenetik dan molekuler. Goal dari terapi adalah mencapai respon sitologik komplit (CCyR) dalam 12 bulan terapi dan bahkan mecapai mayor moleculer respon (MMR) untuk mencegah transformasi atau krisis blastik.

Respon Hematologik

*Complete hematologic response* (CHR) didefinisikan sebagai respon dengan hasil pada darah tepi tanpa adanya sel yang immature, jumlah lekosit kurang dari 10 x 10⁹/l dan jumlah platelet kurang dari 450 x 10⁹/l. Pasien tanpa gejala klinik dan splenomegali menghilan. Partial hematologic response bila dijumpai adanya penurunan sel yang imatur dan atau platelet kurang dari 50% dari sebelum terapi dan atau splenomegali yang persisten atau mengalami pengecilan tetapi kurang dari 50%.

Cytogenetic Response


Respon sitogenetik merupakan respon yang paling banyak dipakai untuk menilai respon CML. Pencapaian respon terapi ini merupakan faktor
prognostik yang penting dari angka harapan hidup penderita. Pasien yang mencapai minor cytogenetic response dalam 3 bulan, PCyR dalam 6 dan 12 bulan dan CCyR dalam 18 bulan dihubungkan dengan respon CCyR jangka panjang.

**Molecular Response**

Molekuler response ditentukan oleh jumlah BCR-ABL chimeric RNA. RT-PCR (*reverse transcriptase polymerase chain reaction*) merupakan cara yang sangat sensitive untuk mengukur BCR-ABL chimeric RNA. Melalui cara ini dapat diukur transkrip BCR-ABL melalui sumsum tulang atau darah tepi. Hasil RT-PCR adalah kualitatif yaitu positif atau negatif.

Major molecular response (MMR) ditentukan oleh penurunan 3-log atau lebih dari transkrip BCR-ABL dari standar dasar. Sedangkan complete molecular response (CMR) terjadi apabila tidak terdeteksi chimeric RNA BCR-ABL melalui test QPCR. Sebagian besar pasien yang mendapatkan imatinib, nilotinib, dasatinib dan allogenic HSCT akan mencapai CCyR dan sedikit CMR. Transkrip BCR-ABL akan menurun pelan-pelan setelah tercapai respon sitogenetik yang komplit. Oleh karena itu QPCR penting untuk monitoring setelah tercapainya CCyR.

**ARAH TERAPI YANG AKAN DATANG**


Meskipun mekanisme residual disease tidak diketahui, pengembangan obat-obatan yang mengatasi masalah tersebut terus dilakukan. Pengembangan vaksin terhadap peptide BCR-ABL sedang dalam
evaluasi. Dengan peningkatan keberhasilan HCT, kombinasi terapi ini dengan terapi non-transplan atau imunoterapi mungkin memberikan hasil yang lebih baik.

DAFTAR PUSTAKA

UPDATE ON TRANSFUSION MEDICINE

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A blood transfusion is the transfer of blood or blood products from one person (donor) into another person's bloodstream (recipient). This is usually done as a lifesaving maneuver to replace blood cells or blood products lost through severe bleeding, during surgery when blood loss occurs or to increase the blood count in anemic patient. Blood transfusion is one aspect of study that we learned at transfusion medicine. It is the branch of medicine that is concerned with the transfusion of blood and blood components, the blood bank, and all of the people that included like a system.

The systems and processes involved in the transfusion pathway are very complex. Organisations should focus on simplifying procedures and concentrate on key steps. Only staff who are trained and competent should participate in blood transfusion process. British Committee for Standards in Haematology (BCSH 2009). The guidance is not wholly evidence-based but built on recommendations to improved the safety of blood ordering and administration from current national guidelines and serious Hazards of transfusion. The transfusion must be right blood, right patient, right time. These regulations set the standards for quality and safety for the collection, testing, processing storage and distribution of human blood components. These are two aspects of regulations which directly impact on practitioners involved in clinical transfusion process:

Traceability asserts that we must have unambiguous evidence of the final fate of every blood component issued from the transfusion services, and that the record is kept for 30 years.

Haemovigilance reporting requires that any serious adverse event or serious adverse reaction, which might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in or prolongs hospitalization or morbidity.

Depend to transfusion risks and problem happen on blood transfusion, improve knowledge about donor, collecting, testing, preparing
blood component, using apheresis technology medicine how to do blood transfusion effective efficient and humanistic must be updated with continuing education program.

Dipresentasikan pada semiloka BLOOD ke 2 di Hotel Haris Denpasar 1 Agustus 2015
EPIDEMIOLOGI, PATHOPHYSIOLOGI AND MANAJEMEN VENOUS THROMBOEMBOLISM (VTE): FOKUS PADA RIVAROXABAN SEBAGAI SUATU NEW ORAL ANTICOAGULANT

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DVT dan komplikasinya berupa emboli paru atau pulmonary embolism (PE) adalah dua ekspresi dari satu kesatuan penyakit yang disebut sebagai thromboemboli vena atau venous thromboembolism (VTE). Thrombosis vena dalam atau deep vein thrombosis (DVT) adalah terjadinya thrombosis pada lumen vena dalam (vena profunda). Sedangkan emboli paru (Pulmonary Embolism = PE) adalah terjadinya penyumbatan pembuluh paru oleh emboli yang berasal dari lepasnya thrombus dari DVT. Oleh karena morbiditas, mortalitas dan biayanya yang tinggi, VTE merupakan masalah kesehatan utama di negara-negara Barat. VTE merupakan penyebab kematian yang sering dapat dicegah. VTE merupakan penyebab kematian ketiga setelah stroke dan infark miokard. Insiden VTE adalah 1,43 per 1000 penduduk per tahun, dan untuk DVT adalah 0,93 per 1000 penduduk per tahun, sedangkan untuk PE adalah 0,5 per 1000 penduduk per tahun. Insiden meningkat secara eksponensial dengan meningkatnya umur.

Prinsip dari triad Virchow’s yaitu kerusakan endotil, stasis aliran darah dan hiperkoagulabilitas merupakan dasar patogenesis dari VTE. Stasis dan kerusakan endotil penting pada DVT setelah trauma dan pembedahan, sedangkan hiperkoagulabilitas bertanggung jawab untuk kasus DVT spontan. Pada orang dewasa, keadaan-keadaan yang merupakan predisposisi atau faktor risiko VTE adalah umur lanjut, kanker beserta pengobatannya, imobilitas, stroke atau paralisis, riwayat VTE sebelumnya, gagal jantung kongestif, infeksi, kehamilan dan puerperium, pil kontraseptif, dan penerbangan jarak jauh. Faktor risiko genetik dibagi menjadi faktor risiko kuat, moderat dan ringan. Faktor risiko yang kuat adalah: defisiensi anti-thrombin, defisiensi protein C dan protein S. Faktor risiko moderat adalah faktor V Leiden, prothrombin 20210A, dan fibrinogen...
10034T. Faktor risiko yang lemah adalah varian fibrinogen, faktor XII dan faktor XI.

DVT terbentuk pertama kali dalam kantong katup vena oleh karena stasis dan hipoksia. Thrombosis terjadi jika aktivasi faktor koagulasi melebihi kapasitas antikoagulan natural dan sistem fibrinolitik. Gejala DVT disebabkan karena obstruksi aliran vena dan peradangan pembuluh darah dan jaringan perivaskuler. Gejala klinik berupa pembengkakan tungkai bawah, nyeri dan nyeri tekan pada betis. Gejala ini tidak sepenuhnya dapat dipercaya sehingga memerlukan pemeriksaan lain untuk menegakkan diagnosis DVT. VTE dibagi menjadi 2 golongan besar: (1) provoked VTE dan (2) unprovoked VTE. Provoked VTE adalah VTE yang dapat diketahui faktor penyebabnya, baik yang bersifat transient, seperti pembedahan dan hospitalisasi, ataupun yang irreversible seperti kanker. Sedangkan unprovoked VTE adalah VTE yang tidak diketahui faktor penyebabnya (idiopatik).


Tujuan pengobatan DVT adalah untuk mencegah kematian karena emboli paru, mengurangi kesakitan karena DVT, dan mengurangi sindroma postphlebitik dan komplikasi lainnya. Semua tujuan ini dapat dicapai dengan pemberian antikoagulan yang adekuat. Tiga prinsip dasar terapi adalah: pertama, berikan antikoagulan secara parenteral dengan dosis efektif segera setelah diagnosis ditegakkan; kedua, antikoagulan awal harus menggunakan obat parenteral beraksasi cepat; ketiga, penderita harus menerimaosisis terapeutik penuh, karena dosis subterapeutik disertai risiko tinggi terjadinya kekambuhan DVT.

Terapi berupa heparin berberat molekul rendah dengan dosis disesuaikan berat badan, diberikan subkutan dua kali sehari. Tidak
diperlukan pemantauan efek antikoagulan. Pilihan kedua adalah un\textit{fractionated heparin} dengan dosis disesuaikan untuk mencapai rasio APTT 1,8 sampai 2,5. Fondaparinux, suatu anti faktor Xa langsung telah dilaporkan sama efektifnya seperti heparin berberat molekul rendah. Penggunaan heparin disertai pemberian warfarin oral pada hari yang sama. Heparin diberikan paling sedikit 4 hari, sampai tercapai INR 2,0 sampai 3,0 pada dua hari berturut-turut. Pada sebagian besar penderita DVT pemberian terapi warfarin jangka panjang dapat mencegah sebagian besar kekambuhan. Pada DVT pertama kali dalam konteks faktor risiko sementara seperti operasi atau trauma pemberian warfarin selama 3 bulan sudah memadai. Pada DVT pertama kali dengan faktor risiko tidak dapat diidentifikasi (idiopatik) pemberian heparin minimum 6 bulan. Terapi yang diperpanjang (lebih dari 6 bulan) dapat dipertimbangkan pada kasus DVT yang mengalami kekambuhan atau jika faktor risiko tetap berlangsung. Untuk DVT pada penderita kanker heparin berberat molekul rendah dilaporkan lebih baik dibandingkan dengan warfarin pada terapi jangka panjang.

Akhir-akhir ini, dikembangkan obat antikoagulan oral baru (\textit{new oral anticoagulants} = NOACs), seperti penghambat langsung faktor Xa (rivaroxaban dan apixaban) dan penghambat langsung thrombin (dabigatran). Uji klinik menunjukkan NOACs sama efektifnya atau lebih efektif dibandingkan dengan warfarin untuk terapi antikoagulan jangka panjang. Rivaroxaban adalah \textit{direct anti-Xa}. Rivaroxaban (Xarelto\textsuperscript{5}) telah diuji klinik pada \textit{ODIXa-DVT study} dan \textit{EINSTEIN DVT study}, yang membandingkan pemakaian rivaroxaban dan enoxaparin/VKA. Pada penderita yang menderita DVT simtomatik akut tanpa gejala PE, didapatkan bahwa rivaroxaban tidak lebih inferior dibandingkan dengan regimen enoxaparin/VKA (\textit{hazard ratio} – \textit{HR} = 0,68). Keamanan obat (efek samping utama) tidak berbeda di antara 2 kelompok (dengan HR=0,97). Efikasi dan keamanan rivaroxaban konsisten tidak tergantung pada umur, berat badan, jenis kelamin, klirens kreatinin dan adanya kanker. Tidak ada bukti toksisitas pada hati. Dari studi ini disimpulkan bahwa rivaroxaban oral 15 mg 2 kali sehari selama 3 minggu diikuti dengan rivaroxaban 20 mg sekali sehari memberikan terapi yang lebih sederhana, pendekatan obat tunggal untuk terapi DVT akut. \textit{EINSTEIN study} dilanjutkan dengan \textit{EINSTEIN extension study}.
VTE merupakan keadaan yang serius dan potensial mengancam jiwa. Terapi standar saat ini adalah pemberian LMWH atau UFH secara parenteral atau fondaparinux diikuti dengan pemberian obat anti vitamin K (VKAs) oral. Pemakaian VKA tidak praktis karena memerlukan pengaturan dopsis sesuai hasil pemeriksaan INR, sehingga kepatuhan penderita rendah. Untuk pengobatan *unprovoked* atau VTE dengan faktor risiko permanen memerlukan obat pemeliharaan sampai bertahun-tahun dengan VKA atau LMWH. Riovaroxaban sebagai NOACs telah memberikan harapan baru bagi terapi jangka panjang yang lebih sederhana sehingga meningkatkan kepatuhan penderita. Studi EINSTEIN menunjukkan rivaroxaban tidak lebih inferior dari regimen LMWH/VKA dalam hal efikasi dan keamanan obat. Namun demikian diperlukan data-data yang lebih banyak sehingga pemakaian rivaroxaban pada VTE disertai evidence-based yang kuat.
MAKALAH
BEBAS
THE ASSOCIATION BETWEEN HEMOGLOBIN LEVEL WITH DISEASE SEVERITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN RSUP SANGLAH

Putu Cyntia Ratnadi, Ketut Suega, Renny A Rena

**Background.** Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a wide spectrum of manifestations. Anemia was one of the hematologic manifestations of SLE that occurred frequently due to suppression of erythropoiesis by the presence of chronic inflammation. Severity of anemia often reflected an underlying condition, including SLE. The lower levels of hemoglobin (Hb), usually related to more severe underlying disease.

**Objective.** To determine the association between Hb level with disease severity in patients with SLE.

**Methods.** This study was an observational analytic study with case studies of cross-sectional study. The sample were SLE patients who treated in RSUP Sanglah, Denpasar. We observed medical records SLE patients in the period of January-December 2014. The independent variable was severity of SLE and dependent variable was hemoglobin level. Statistic analysis used chi square.

**Results.** Forty one patients aged 17-74 y.o, mean 33.46±11.61 y.o were included in this study. Majority of SLE subjects were woman (92.7%). Hb level was ranging from 3.00-16.10 g/dl, mean 10.09±2.92 g/dl. Low Hb level was occurred in 29 subjects (70.7%), 9 (47.4%) in mild disease and 20 (90.0%) in severe disease respectively. The association between Hb level with severity of SLE was statistically significant (p<0.05).

**Conclusions.** Hb level was significantly related to disease severity in patients with SLE in RSUP Sanglah.

**Keywords.** Hemoglobin level, disease severity, systemic lupus erythematosus
THE PROGNOSIS OF NON-HODGKIN LYMPHOMA PATIENTS TREATED WITH FIRST-LINE CHEMOTHERAPY BASED ON IPI SCORE IN SANGLAH GENERAL HOSPITAL 2014

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Background: Non-Hodgkin Lymphoma (NHL) is a malignant hematological disease originates in the lymphocytes, caused by abnormality in lymphocytes development which forms tumor and may become cancer. International Prognostic Index (IPI) Score is clinical tool which aid in predicting the prognosis of NHL patients, using several components such as age, stage of disease, level of Lactate Dehydrogenase (LDH) serum, extranodules engagement, and performance status.

Objectives: To measure the prognosis of NHL patients treated with first-line chemotherapy based on IPI score in Sanglah General Hospital 2014.

Methods: This study used a retrospective descriptive study on NHL patients in Sanglah General Hospital 2014. The patients received various combinations of first-line chemotherapy. Evaluation was measured using IPI score to determine the prognosis of patients.

Results: Twenty-five patients were included in the study. Age-span was between 61-76 years old (Mean 65,68 ± 4,7 years; Median 65 years). The number of male patients was 19 (76%). NHL clinical symptoms found in the patients are characterized by the presence of a lump (100%), fever (80%), weight loss (80%), fatigue (80%), anemia (72%), and organ complaints (52%). Diffuse Large B-Cell Lymphoma (DLBCL) is the most common histopathological structure observed on the patients (68%). The IPI scores result consists of four patients (16%) in low risk category, two patients (8%)
in low-intermediate risk category, two patients (8%) in high-intermediate risk category, and 17 patients (68%) in high risk category.

**Conclusion:** Most of NHL patients in Sanglah General Hospital Denpasar were having poor prognosis status.

**Keywords:** Prognosis, Non-Hodgkin Lymphoma, IPI Score
Characteristic of Chronic Myeloid Leukemia Patients in Sanglah Hospital on 2014-2015

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Background: Chronic Myeloid Leukemia is a disorder that caused by translocation of chromosomes 9 and 22. In Sanglah Hospital, there are pretty much incidences of Chronic myeloid leukemia. There are some characteristic of the patients that can be observed.

Aim: To know the characteristic of CML patients in Sanglah Hospital Denpasar on 2014-2015.

Method: This study used total sampling method. The samples were all patients that had been diagnosed and still seek a medications on 2014-2015. The information was obtained from their medical record, such as gender, age, CML phase, clinical manifestation, history of blood transfusion, Complete Blood Count, BCR-ABL qualitative, and medication history (tyrosine kinase inhibitor/non tyrosine kinase inhibitor).

Result: In this study, 42 cases met inclusion criteria and included as a samples. There were 28 males (66.7%). The mean of age was 37.74±14.27 years old. There were 39 samples (92.9%) in chronic phase, and 3 samples (7.1%) in acceleration phase. Clinical manifestation that had been showed are fever 24 samples (57.1%), decreased body weight 39 samples (92.9%), anemia 35 samples (83.3%), bleeding 15 samples (35.7%), splenomegaly 38 samples (90.5%), and hepatomegaly 11 samples (26.2%). The mean of leukocyte, hemoglobin, and thrombocyte were 236.22 x10^3/µl, 9.23 g/dl, and 433.64x10^3/µl. There were 25 samples (59.5%) did blood transfusion. In this study 35 samples (83.3%) had positive BCR-ABL qualitative. The
medication history were TKI only: 13 samples (31%), non-TKI only: 7 samples (16.7%), and both 22 samples (52.4%).

**Conclusion**: Males was dominant, decreased body weight as most common clinical manifestation and most cases in chronic phase.

**Keywords**: Characteristic, CML, gender, age, CML phase, clinical manifestation, blood transfusion, CBC, BCR-ABL qualitative, TKI, non-TKI.
Prevalence of Patients Aplastic Anemia who Treated in Internal Medicine Polyclinic RSUP Sanglah Denpasar on 2014

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Introduction: Aplastic anemia (AA) is a bone marrow disorder that characterized by pansitopenia in the peripheral blood and bone marrow cellularity decrease. In this condition, the production of number bloods cells is inadequate. Patients had pancytopenia, in this condition occur decrease number of red blood cells, white blood cells and trombocys.

Purpose: To know about prevalence of aplastic anemia’s patient in RSUP Sanglah and to know about prevalence of severe and non-severe aplastic anemia’s patient in RSUP Sanglah.

Methods: This research use descriptive study’s methods in aplastic anemia’s patient in the RSUP Sanglah on 2014. Personal data of aplastic anemia’s patient get from medical record in RSUP Sanglah, there are sex, age, number of blood’s component such as white blood cells, hemoglobin, trombocyts and neutrophils, and the class of anemia aplastic.

Result: The result of this research is prevalence 10 aplastic anemia patient who according with inklusion scale. From this research which dominant sample is woman: 6 person (60%). Age of aplastic anemia’s patient from 16-75 year with average of the age is 47±17.85 year. Clinical manifestation of the sample shown symptom is limp. Examination of Aplastic Anemia’s diagnose get from blood examination in the laboratory. This examination to know about number component of blood that inadequate. Result of first laboratory examination is average of leukocyt: $2.65 \times 10^3/\mu L$, average of hemoglobin: $7.57 \, \text{g/dL}$, average of trombocyt: $61.89 \times 10^3/\mu L$, average of neutrofil: $1.14 \times 10^3/\mu L$. Classification of this sample are 4 (40%) person for Aplastic Anemia’s Severe and 6 (60%) for aplastic anemia’s non-severe.
Conclusion: Prevalence of aplastic anemia’s patient in RSUP Sanglah are 10 person, which dominant result is woman there are 6 person (60%). From 10 person aplastic anemia’s patient can be classified become aplastic anemia’s non – severe get 4 person and aplastic anemia’s severe get 6 person.

Key Word: Aplastic Anemia, Non-Severe and Severe, Prevalence of Aplastic Anemia.
HEMATOLOGY RESPONSE CHRONIC MYELOID LEUKEMIA PATIENT WHO GETS TYROSINE KINASE INHIBITOR TREATMENT FOR A YEAR IN GENERAL HOPITAL CENTER SANGLAH

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Background: Chronic Myeloid Leukemia (CML) is disorder that cause by reciprocal translocation between chromosome 9 and 22, that produce cimeric oncogene called BCR-ABL, which is the product of protein Tyrosine Kinase and cause uncontrolled proliferation of myeloid cell. Tyrosine Kinase Inhibitor (TKI) work to inhibit BCR-ABL gene, so as to produce in hematologic remission.

Objective: To determine the hematologic response of CML patient who received treatment TKI for a year.

Method: This study used a retrospective descriptive method against CML patient in Sanglah Hospital. Chronic Myeloid Leukemia patient evaluated to determine the hematologic response after used TKI for a year. Evaluated is done from the beginning diagnosed, 3 month, 6 month, 9 month, and 12 month. The information obtained from medical record and interviews.

Result: Of the 29 patient who responded had a lifespan of 18-75 years with a mean age 36,76 ± 13 years. Nineteen people (65,5%) were male. The mean result of leukocyte prior TKI therapy 227,59 ± 22,03 x 10³/mm³ be 14,61 ± 3,45 x 10³/mm³ after 12 months receive TKI. The mean hemoglobin prior TKI 9,68 ± 0,42g/dL be 12,07 ± 0,42 g/dL after 12 month receive TKI. The mean thrombocyte prior TKI 458,32 ± 86,35 x 10³/mm³ be 276,79 ± 29,68 x 10³/mm³ after 12 month receive TKI.
Conclusion: The result of the study showed an improvement of hematologic response CML patient who receive TKI for a year. Decrease in the mean leukocyte, an increase in the mean hemoglobin, and decrease in the mean thrombocyte.

Key Word: Hematologic Response, Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitor
AGE AND GENDER FACTOR ASSOCIATED WITH NON-HODGKIN LYMPHOMA EVENTS IN SANGLAH HOSPITAL DURING 2014

Ida Ayu Cili Swesis, Ketut Suega, Renny A Rena

Background: The incidence of non-Hodgkin's lymphoma (NHL) had increased dramatically since 1970 at the rate of 5-10% each year. In Indonesia, NHL is ranked sixth most frequent disease of all malignancy. Nowadays, still no explanation for the increasing incidence of NHL. Several risk factors were believed to be the cause of NHL. Two of them were age and gender.

Objective: To identify the association between age and gender with the incidence of NHL in Sanglah Hospital 2014

Methods: The retrospective cross sectional design was used in this research. Sampel were Non Hodgkin Lymphoma patients who treated in Sanglah Hospital during January-December 2014. The dependent variable were the incidence of NHL and non-NHL events and independent variables were gender and age.

Results: In 2014, 152 cases of NHL with male respondents 57.9% treated at Sanglah Hospital. Subjects age ranging from 1-89 y.o, with median age 55 y.o. In Chi-square analysis, there was a significant association between age with NHL incidence in Sanglah Hospital (p <0.05) and no significant association between the gender with NHL incidence (p> 0.05).

Conclusion: There was a significant association between age with NHL incidence and gender wasn’t have a significant association with the incidence of NHL in Sanglah Hospital.

Keywords: Age, Gender, Non-Hodgkin's Lymphoma, Sanglah Hospital
CLINICAL CHARACTERISTICS OF CHRONIC MYELOID LEUKEMIA PATIENTS WITH TYROSINE KINASE INHIBITOR THERAPY IN SANGLAH HOSPITAL YEAR 2011-2014

Gabrielle A Kartawan, Ketut Suega, Renny A Rena

Introduction: Chronic Myeloid Leukemia (CML) is the most common type of leukemia in Indonesia. Tyrosine Kinase Inhibitor (TKI) is now the main therapy for CML. However, data about clinical characteristics and TKI usage in CML patients are still rare in Indonesia. This study aims to evaluate clinical characteristics, peripheral blood count, complete hematologic response (CHR) and adverse effects of TKI in CML patients.

Methods: This is a retrospective cross-sectional study using medical record of CML patients with TKI therapy in RSUP Sanglah during 2011-2014. Twenty nine patients met the criteria.

Results: All 29 patients were in chronic phase and 19 of them were males. Median age was 36 years. The most common manifestations were weight loss (100%) and splenomegaly (96%). Imatinib was administered in 21 patients and the rest received nilotinib. Before TKI was administered, median WBC was 118.500/mm$^3$, Hb was 9,5 g/dL, and platelet 338.000/mm$^3$. After 3 months of therapy TKI, median WBC was 14.500/mm$^3$, Hb was 10,9 g/dL, and platelet was 124.400/mm$^3$. Within 3 months of TKI therapy, 13 patients (44,8%) achieved CHR. The most common non-hematology adverse effect was nausea (62,1%) and hematology adverse effect was anemia (37,9%).

Conclusion: In this study, splenomegaly was the most notable manifestation of CML. CHR in 3 months was lower compared to other studies. Percentage of nausea, hypopigmentation, anemia and neutropenia were higher in patients with imatinib. Percentage of myalgia and thrombositopenia were higher in patients with nilotinib.

Keywords: Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitor, complete hematologic response, Sanglah Hospital
PREVALENCE OF ANEMIA IN CHRONIC KIDNEY DISEASE PATIENTS WITH AND WITHOUT DIABETES MELLLITUS IN SANGLAH HOSPITAL, DENPASAR-BALI

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Introduction: Chronic Kidney Disease (CKD) is the ninth leading cause of death in United State. It is high prevalent disease, mostly caused by Diabetes Mellitus (DM). Anemia is the cardinal feature of Chronic Kidney Failure, prior to the other complications. This study aims to evaluate anemia in CKD patient with and without DM.

Methods: During March-July 2015, a cross-sectional study was conducted using consecutive sampling method. Medical records of CKD patients with and without DM were evaluated to assess the hemoglobin level in first visit. Data were analyzed using bivariate analysis.

Results: Sample of this study were 174 CKD patient (age 18-75 years old, mean 53,87±11,45), with 102 patients were male. Prevalence of anemia in CKD (stage I-V) with DM vs without DM were (in percent) : 1,5 vs 0; 4,4 vs 0;16,2 vs 0; 11,8 vs 2,6; 66,2 vs 97,4 (chi square p<0.001). Between two groups, mean value of hemoglobin show not significantly differ (9,12±2,38 for diabetes vs. 9,79±23,07 for non diabetes) by independent sample t test (p=0,107). Chi square analysis show significant (p=0.025) for higher percentage of anemia in CKD patient with DM (68.7% vs 52.0%)

Conclusion: DM was correlated with anemia and may be linked to premature expression of anemia in CKD. Anemia is significantly more common in diabetic patients and has higher severity than observed in nondiabetic patient. The prevalence of anemia in diabetic patient is dominant compared to in non-diabetic patients in stage I-IV of CKD.

Keyword: anemia, chronic kidney disease, diabetes mellitus