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Meeting abstracts

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MEETING REPORT

II

What's new in the management of chronic lymphocytic leukemia? 2008 ASH Review (New York Medical College, January 31, 2009)

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The 2008 ASH Annual Meeting featured several important abstracts highlighting advances in the treatment of chronic lymphocytic leukemia (CLL).

Abstract 43 [1] retrospectively compared results of a phase II study of pentostatin and rituximab (PR) to previously published results using pentostatin, cyclophosphamide and rituximab (PCR) [2]. The pentostatin dose was increased to 4 mg/m² in the PR regimen, but demographics of patients in both studies were similar [1]. Overall response rate (OR) and complete response (CR) rates were similar for PR (79%, 30%) and PCR (91%, 41%), but median progression free survival (PFS) was significantly shorter for PR (12 months vs. 31 months) [1]. These results supported previous findings that the addition of cyclophosphamide to fludarabine improves OR, CR and PFS [3–5].

Abstract 325 presented results of the German CLL Study Group (GCLLSG) CLL8 study randomizing 817 previously untreated patients to fludarabine and cyclophosphamide (FC) or fludarabine, cyclophosphamide and rituximab (FCR) [6]. OR, CR and median PFS favored FCR (93%, 45%, 43 months) over FC (85%, 23%, 32 months), although 2-year overall survival (OS) was similar (91% vs. 88%). Abstract 326 demonstrated that median PFS depended upon the ability to eradicate minimal residual disease (MRD) in the peripheral blood, with PFS increasing from 15 months (MRD $\geq 10^{-2}$) to 34 months ($10^{-4} \geq$ MRD $> 10^{-2}$) to not reached (MRD $< 10^{-4}$) with increasing eradication of MRD [7]. Furthermore, 67% of patients receiving FCR achieved MRD $< 10^{-4}$, compared to only 34% of FC patients, thus accounting for the improved PFS with FCR.

Abstract 327 randomized 184 patients (80% previously untreated, 20% relapsed) to PCR or FCR, using the MSKCC PCR regimen (pentostatin dose 4 mg/m²) and the Johns Hopkins

FCR regimen (fludarabine 20 mg/m² days 1–5, cyclophosphamide 600 mg/m² day 1). The primary endpoint, incidence of grade 3–4 infections, was similar for PCR (34%) and FCR (31%). Only 50% of patients in both arms completed therapy, resulting in surprisingly low OR and CR rates for PCR (45%, 7%) and FCR (58%, 17%). The trial was stopped early, so there were no statistically significant differences between the two arms, and no PFS data was presented. Nonetheless, abstract 327 indicated that results from academic centers may not necessarily be reproducible in the community [8].

Abstract 2095 updated results of a phase II study of cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) in 48 previously untreated patients with high-risk features [9]. OR and CR were 94% and 69%, respectively, with OR 77% and CR 54% in 13 patients with del (17p13). Grade 3–4 neutropenia and thrombocytopenia were observed in 71% and 42% of patients, respectively, and 6% and 27% of patients developed major and minor infections, respectively.

Abstract 2091 updated results of a phase III study randomizing 319 previously untreated patients to chlorambucil or bendamustine [10]. OR, CR and median PFS favored bendamustine (67%, 32%, 21.5 months) over chlorambucil (30%, 2%, 8.3 months), although bendamustine caused greater hematologic toxicity (40% vs. 19%), especially grade 3–4 neutropenia (23% vs. 9%).

Two studies of lenalidomide in previously untreated patients were presented [11, 12]. Abstract 44 summarized results of a phase I study in 25 Canadian patients [11]. Due to grade 5 sepsis and grade 3–4 tumor lysis, the dose was decreased from 25 mg to 2.5 mg and then escalated to 10 mg daily for 21 days every 28 days. Toxicity included fatigue (78%), tumor flare (78%), rash (48%) and grade 3–4 neutropenia (43%). OR and CR were 65% and 0%, respectively. Abstract 45 presented a study in 43 elderly patients age 65 or older [12]. Lenalidomide was given continuously, and 5–10 mg daily was the median delivered dose. Grade 3–4 myelosuppression and tumor flare were observed in 26% and 44% of patients, respectively. OR and CR were 54% and 0%, respectively. While lenalidomide is clearly active in CLL, the absence of CR in previously untreated patients was disappointing.

Abstract 47 presented a phase II study giving high dose methylprednisolone 1000 mg/m² day 1–3 every four weeks and weekly rituximab (total dose 4500–6750 mg/m²) to 28 patients [13]. OR and CR were 96% and 32%, respectively. Patients were

lesser splenomegaly and lower beta-2-microglobulin levels were more likely to respond.

In the relapsed setting, abstract 329 presented final results of the GCLLSG CLL2H study which administered subcutaneous alemtuzumab to 103 relapsed patients, many of whom had high-risk features [14]. Infusion toxicity was minimal, but grade 3–4 anemia (56%), thrombocytopenia (57%), anemia (49%), cytomegalovirus reactivation (8%) and non-CMV infection (29%) were significant toxicities. Seventy-five patients died; 56% died of progressive CLL, and 31% died of infection. OR (34%), CR (4%) and median PFS (7.7 months) were similar to the results achieved by intravenous alemtuzumab in the pivotal CAM211 study [15]. Abstract 330 summarized a phase II GCLLSG trial administering bendamustine 70 mg/m² on day 1–2 and rituximab 500 mg/m² on day 1 to 81 relapsed CLL patients [16]. OR and CR were 77% and 15%, respectively. Twelve of 13 patients (92%) with del (11q22), 4/9 patients (44%) with del (17p13), and 29/39 patients (74%) responded, indicating that bendamustine is active in high-risk relapsed CLL.

Abstract 46 presented combined phase I/II results of flavopiridol (alvocidib) in 116 relapsed patients, 70% of whom were fludarabine-refractory [17]. OR in this high-risk population was 47%. Furthermore, 19/39 del (17p13) patients (49%), 28/47 del (11q22) patients (60%) and 22/52 complex karyotype patients (42%) responded, demonstrating the activity of flavopiridol in poor-risk groups with limited therapeutic options. Forty-one of 85 patients (48%) with bulky lymphadenopathy >5 cm responded. Median PFS in responders was 10–12 months across all risk groups. A registration study is ongoing.

Finally, abstract 328 presented a pivotal phase II study of the fully humanized anti-CD20 antibody ofatumumab (HuMax-CD20) in relapsed patients refractory to both fludarabine and alemtuzumab (DR, n = 59) or with bulky lymphadenopathy refractory to fludarabine (BFR, n = 79) [18]. OR, time to next therapy, and OS were similar for the DR (51%, 9.0 months, 13.7 months) and BFR groups (44%, 7.9 months, 15.4 months). These results have been submitted for FDA approval.

Competing interests: The authors declare that they have no competing interests.

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MEETING ABSTRACTS

AI

Molecular target therapy – towards curative regimen: a 20-year experience in the treatment of acute promyelocytic leukemia (APL) in the Shanghai Institute of Hematology

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Since the first description of acute promyelocytic leukemia (APL) in 1957 as the most malignant form of acute leukemia, several developments have paved the way to make this disease the most curable leukemia in adults and change the paradigm of cancer

treatment. Therapy of APL was pioneered by Bernard et al in 1973 demonstrating a striking sensitivity to daunorubicin, probably related to significantly lower P-glycoprotein expression observed in APL cells compared to other subtypes of acute myeloid leukemia (AML).

The incorporation of ATRA, a noncytotoxic differentiating agent that is regarded as the first differentiation therapy has changed dramatically the management, outcome, and prognosis of APL.

ATRA was first introduced to clinical use for the treatment of APL in 1986. Since then, randomized studies in many centers around the world document a rising CR rate, a decrease in severe adverse effects, and a prolongation of remission duration. ATRA combined with anthracycline-based chemotherapy can achieve CR in 90–95% of patients with APL and cure the disease in 70–75% of the cases. Combination therapy with ATRA and chemotherapeutic agents should now be considered as a standard treatment of APL.

Over the last decade, tremendous efforts have been made to elucidate the molecular genesis of APL, as well as the mechanism of action of ATRA. The mechanism of action of ATRA can be summarized as follows: 1. The binding of ATRA to RAR receptors causes degradation of PML-RAR α protein through the ubiquitin-proteasome and caspase system, leading to restoration of terminal differentiation of promyelocytes; 2. Exposure of APL cells to ATRA in vitro or in vivo induces relocalization of PML and restores the normal structure of PODs; and 3. Under the action of ATRA, CoR is dissociated from the repressive complex, whereas CoA (coactivator) is recruited to the complex. As a result, the repression of transcriptional activation of target genes is relieved and the differentiation of promyelocytes is restored.

Treatment of APL by arsenic compounds represents a successful example of apoptosis induction therapy of acute leukemia. As₂O₃ exerts dual effects on APL cells. Studies in vitro with NB4 cells showed that a higher concentration of As₂O₃ (0.5–1.0 μ M) induced apoptosis with typical morphological changes, DNA laddering on agarose gel electrophoresis, appearance of an apoptotic peak on flow cytometric analysis, and increased expression of annexin V on the cell surface membrane. At lower concentrations, As₂O₃ can induce APL cells to partially differentiate along the granulocytic pathway.

Synergistic effect of ATRA and As₂O₃ was confirmed by several research works in vivo and in vitro. The first clinical trial was completed by SIH in 2001. CR rate was same as ATRA or As₂O₃ alone, but the median day to CR was very short, only 26 days, and OS and DFS were much better than ATRA or As₂O₃ alone. Now timing and dose of As₂O₃ combined with ATRA in newly diagnosed APL patients need to be confirmed.

Recently, several genetic and phenotypic characteristics of acute promyelocytic leukemia (APL) blasts have been demonstrated. These include the PML/RAR α fusion and the transcription co-repressor complex recruited at the promoter of target genes by the hybrid protein, the intense and homogeneous expression of the CD33 antigen, and absence of multidrug resistance-related phenotype, a frequently mutated and constitutively activated FLT3 receptor. Such genotypic and phenotypic features are targeted by agents currently in use in front-line therapy or at relapse (i.e., retinoids, As₂O₃, anthracyclines and anti-CD33 monoclonal antibodies), and by novel agents that may find a place in future treatments such as histone deacetylase and FLT3 inhibitors.

A2 Update of recent studies in chronic myeloid leukemia

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The use of tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes for patients with chronic myeloid leukemia (CML). The IRIS study is the definitive phase III trial of imatinib mesylate as frontline therapy for CML. Seven year follow-up data has recently been reported [1]. The overall survival (including deaths from all causes) is 86% and the event free survival is 81% at seven years. Seven percent of patients have progressed to accelerated or blastic phase, with the highest risk being in the second year of treatment. Eighty-two percent of patients have achieved complete cytogenetic remission (CCyR) and 83% of these patients maintain that remission. Of the patients that discontinued study, 8% were for toxicity, 15% for efficacy and 17% for other reasons.

In the United States, the FDA approved dose of imatinib for patients in chronic phase is 400 mg daily. However in the original phase I study a true MTD was not determined, and the 400 mg dose was chosen because it was biologically active. More recent data suggests that higher doses may be more efficacious. In the TOPS Trial newly diagnosed patients received either 400 or 800 mg imatinib as front line therapy [2]. The primary endpoint of the study, major molecular remission (MMR) at 12 months, was similar in the two arms. However patients receiving imatinib 800 mg daily achieved complete molecular remission (CMR) faster (8.4 months versus 13.6 months, respectively, $p = 0.0038$) than patients receiving 400 mg of imatinib daily. The Central European Leukemia Study Group performed a similar study, the ISTAHIT study, in which previously treated patients (with agents other than TKIs) received imatinib 800 mg daily versus 400 mg daily for the first 6 months of therapy [3]. After that all patients received 400 mg daily. This study demonstrated that patients receiving imatinib 800 mg achieved a MMR and/or CCyR faster than patients receiving imatinib 400 mg. Another study of high dose versus standard dose imatinib failed to show a statistically significant increase in the percentage of patients achieving MMR [4]. However when patients were analyzed in terms of the dose of imatinib they actually received, the CCyR was 91% for patients receiving 700–800 mg of imatinib, 73% for patients receiving 400–699 mg and only 20% for patients receiving less than 400 mg of imatinib. Whether the faster achievement of MMR will translate into improved long term outcome remains to be determined. When time to response was measured on the German CML Study IV, achievement of MMR by 18 months was a strong predictor of event free survival [5]. Similarly, in a retrospective study from Australia, the early achievement of molecular response was predictive of event free survival [6]. Events occurred in 0/41 patients achieving MMR by 6 months, 3/40 (8%) of patients achieving MMR in 6–12 months, and 5/22 (15%) of patients achieving MMR by 12–18 months.

Prior to imatinib, interferon and ara-C were the mainstays of therapy. The SPIRIT Trial is studying whether the addition of ara-C or pegylated interferon to imatinib will result in an increased percentage of patients with MMR [7]. Although many patients

were unable to tolerate the increased toxicity of the combination therapy, the percentage of patients with MMR was 57% for patients randomized to imatinib plus pegylated interferon versus 38% for patients randomized to imatinib 400 mg as a single agent, $p = 0.0008$. Again, whether this translates into improved long term outcome remains to be determined.

Many patients who progress on imatinib respond to second line therapy with either nilotinib or dasatinib. Nilotinib is an imatinib analogue with more specific BCR/ABL binding. Dasatinib is a dual SRC/ABL kinase inhibitor. Both are effective against a large number of BCR/ABL kinase mutations with the exception of the T315I mutation. Newer studies are evaluating the efficacy of these agents in the front line setting [8, 9]. Both agents lead to high rates of CCyR at 12 months (nilotinib: 93%, dasatinib: 95%, imatinib historical control: 65%, respectively), and MMR at 18 months (nilotinib: 65%, dasatinib: 48%, respectively). Dasatinib toxicity includes pleural effusions in 20% of patients and hemorrhage even in the absence of thrombocytopenia. A change in the dose and schedule of dasatinib to 100 mg orally daily has resulted in a decrease in these toxicities with the maintenance of efficacy. Patients receiving nilotinib require monitoring of QTc, potassium and magnesium to prevent arrhythmias. Further follow up is needed before these agents will be considered standard frontline therapy.

An important question is whether patients with CML can be cured with imatinib. Early reports of pregnant women discontinuing imatinib noted a very high rate of relapse. A more formal study allowed patients who had been in CMR for at least 2 years to stop imatinib [10]. Although half of the patients relapsed rapidly, many of the patients remain in CMR without further therapy. Interestingly, there was trend towards a lower relapse rate in patients who had exposure to interferon prior to imatinib. Most of the patients who relapsed were sensitive to retreatment to imatinib. However it is too early to recommend the discontinuation of imatinib outside of a clinical trial.

A number of new agents are currently under study. Bosutinib is a dual ABL/SRC kinase inhibitor that has minimal inhibition of PDGFR and c-kit. This agent leads to high rates of major cytogenetic and MMR in patients with CML-CP who are imatinib intolerant (51% and 39%, respectively) or resistant (45% and 42%, respectively) [11]. Bosutinib also yields major cytogenetic remissions and MMR in patients who have resistant to both imatinib and dasatinib. Toxicity includes myelosuppression as well as elevations in amylase and lipase. Patients with T315I mutations remain a treatment challenge. Options include aurora kinase inhibitors and allogeneic stem cell transplantation. Omacetaxine mepesuccinate (homoharringtonine) is also being studied [12]. In the past the development of this agent was limited by toxicity, including myelosuppression and the need for prolonged intravenous administration to avoid hypotension. Recently a subcutaneous formulation has been studied in patients with T315I mutations. Complete hematologic remission was seen in 80% of patients in chronic phase and 18% of patients with accelerated phase CML. Toxicity included myelosuppression and febrile neutropenia.

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- A3**
New insights on low-grade and T-cell lymphoma
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- Journal of Hematology & Oncology 2009, 2(Suppl 1):A3*
- The advances in low-grade lymphoma & T-cell lymphoma from the 2008 ASH meeting were presented. These included therapeutic regimens for low grade lymphoma, frontline bendamustine plus rituximab data, radioimmunotherapy consolidation in advanced disease, idiotype vaccine, and other novel therapeutic agents such as next generation anti-CD20 GAI01, syk inhibitor Fostamatinib in treatment of low-grade lymphoma. In T-cell lymphoma, updates were discussed on phase II HOVON 69 trial data of combination of alemtuzumab/CHOP, pralatrexate and romidepsin for relapsed/refractory PTCL, L-asparaginase-containing regimen for extranodal NK/T-cell lymphoma.

A4**Recent progress in the treatment of multiple myeloma: updates and highlights from ASH 2008**

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The treatment of multiple myeloma has rapidly evolved over the past 8 years. During this period we have seen the introduction of two immunomodulatory drugs and a proteasome inhibitor for the treatment of myeloma. Each of these drugs has shown to be effective as single agent as well as in combinations in relapsed and/or refractory myeloma. And the optimum use of these drugs upfront, both for transplant eligible as well as transplant ineligible patients has been the focus of intense clinical investigations as reported by the investigators from US as well as Europe in the last ASH meeting.

A series of large randomized trials have established the addition of a novel agent, either thalidomide or bortezomib, to melphalan and prednisone as the standard of care for transplant ineligible patients. With longer follow-up for a median of 25.9 months VISTA trial showed continued survival benefit for patients randomized to receive upfront bortezomib; three year OS was 72% for VMP compared to 59% for MP. VMP improved outcome in all patients, whether under or over age 75 years, with or without modest renal impairment, as well a patient with adverse prognostic features by cytogenetics or fish. These improvements in outcome came with no difference in hematologic toxicity or HZV infection, but higher incidence of peripheral sensory neuropathy (grade ≥ 3 13%) from bortezomib.

Addition of thalidomide to MP had been shown to improve the progression-free and OS among transplant ineligible patients. However, recent updates of 3 different studies, Italian study (GIMEMA), the Dutch study (HOVON 49) and the Scandinavian study showed improvement in progression-free survival but not OS. This may be related to differences in the dose intensity and tolerability of the treatment, lack of efficacy of thalidomide in high-risk cytogenetic group and availability of other novel agent to rescue upon relapse.

The addition of thalidomide to VMP regimen (VMPT) was compared to VMP in a large randomized trial. In the preliminary analysis after a short follow-up showed no improvement in the PFS or OS but notable increase in toxicity for the four drug combination. The same study showed that weekly administration of bortezomib was well tolerated with much lower incidence of grade ≥ 3 peripheral neuropathy of 2% without significant loss of efficacy.

Earlier reports on ECOG trial E4A03 comparing lenalidomide with low-dose or high-dose dexamethasone highly favored low-dose dexamethasone arm for EFS and OS. However, with longer follow-up (median 36 months) the updated results of the trial showed identical 3-year survival outcome of 75%; but progression-free survival favored low-dose dexamethasone arm. When land mark analysis is performed at the end of four cycles, 3-year survival of patients who proceeded to transplant immediately (N = 90) was 92%; while those who stayed on the primary therapy whether high-dose or low-dose dexamethasone, their 3-year survival was 79%. Thus, lenalidomide and dexamethasone is highly active in newly diagnosed myeloma patients both as an

induction therapy pre-transplant for newly diagnosed myeloma as well as primary therapy for patients ineligible for stem cell transplantation.

Lenalidomide was unable to overcome the adverse prognostic features identified by cytogenetics, FISH or labeling index as noted by a single institutional study of 100 patients with lenalidomide and weekly dexamethasone.

Two large randomized trials have shown bortezomib based induction therapies pretransplant improve the response rate before and after stem cell transplantation and with short follow-up there is improved progression-free survival at 2 years. The first trial was performed by the French investigators (IFM) which compared four cycles of bortezomib and dexamethasone against four cycles of VAD chemotherapy. At the end of induction therapy 39% were in $>$ VGPR after bortezomib-dexamethasone compared to 16% after VAD ($p < 0.0001$). With a median follow-up of 28 months the progression-free survival was superior for the bortezomib and dexamethasone arm with 2 year PFS of 69% vs. 60% for the VAD arm ($p0.011$).

The second trial was reported by the Italian group which compared 3 cycles of thalidomide and dexamethasone (TD) to the same regimen with added bortezomib (VTD). Again, the addition of bortezomib to thalidomide and dexamethasone significantly improved the response rates pretransplant; VGPR or better was 62% for VTD compared to 29% for TD. With a short median follow-up time of 15 months the projected two-year PFS was 90% for VTD arm compared to 80% for TD arm ($p = 0.009$). Other studies have shown replacing the vincristine in the VAD regimen with either thalidomide (TAD) or bortezomib (PAD) also improves the response rate and progression-free survival after transplantation.

In conclusion, advent of novel agents has substantially improved the outcome of patients with newly diagnosed myeloma. MP plus thalidomide or bortezomib should be the choice of therapy for transplant ineligible patients. Brief induction with bortezomib containing regimen is the treatment of choice for transplant eligible patients. Lenalidomide and low-dose dexamethasone is an excellent treatment option for both transplant eligible as well as ineligible patients. Bortezomib has been shown clearly to improve the outcome of patients with high-risk genetic features.

A5**Update on chronic immune thrombocytopenic purpura (ITP)**

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Introduction: Chronic ITP is an autoimmune disorder manifested by immune-mediated platelet destruction and suppressed platelet production. The following article will discuss: normal platelet production and circulation; ITP pathophysiology; and diagnosis and treatment options for ITP.

Platelet production and circulation: Thrombopoietin (TPO), the major cytokine affecting all phases of platelet production, is produced primarily by the liver and binds to the c-Mpl receptor located on platelets, stem cells and megakaryocytes. Upon stimulation, pluripotential stem cells produce cells committed to megakaryocyte differentiation. These cells initially

undergo mitosis followed eventually by endomitosis resulting in a progressive increase in size with cells ranging from 2N to 64N and a proportional cytoplasmic increase. Platelet formation occurs in the cytoplasm and the number of platelets produced/megakaryocyte is roughly proportional to megakaryocyte size. Platelet production is regulated as follows: the liver produces a constant quantity of TPO each day and a large portion of this binds to circulating platelets; unbound TPO is available to stimulate platelet production. In thrombocytopenic states due to reduced platelet production, less TPO is adsorbed by circulating platelets and more is available to stimulate platelet production. In ITP, TPO levels are normal or slightly increased probably due to TPO binding to platelets which are then destroyed, removing TPO from the circulation.

Circulating platelets have an intravascular survival of 7–10 days. About 30% are located in an exchangeable splenic pool which, if enlarged, may result in peripheral thrombocytopenia (e.g., patients with congestive splenomegaly). Platelets are removed from the circulation due to utilization in maintaining vascular integrity or because of old age.

Differential diagnosis of thrombocytopenia: Thrombocytopenia can result from: decreased platelet production, platelet redistribution (enlarged splenic pool) or platelet destruction. Decreased production may be due to myeloproliferative disorders (leukemia, myeloma, etc.), myelodysplasia, aplasia or hypoplasia, drugs (chemotherapy, alcohol, etc.), malignant infiltration or may be inherited. Decreased production is usually diagnosed by evaluation of the blood count and bone marrow. Abnormal platelet distribution involves an enlarged spleen and is most commonly due to congestive splenomegaly although other disorders such as lymphoma, Gaucher's disease, etc. may also have some element of redistribution. There are multiple causes of platelet destruction including infection, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation or immune causes due to alloantibodies, drug-dependent antibodies, acute ITP or chronic ITP or ITP-like syndromes associated with collagen vascular or lymphoproliferative disorders.

Chronic ITP is a diagnosis of exclusion. The classic ITP patient presents with petechiae and easy bruising with or without mucosal bleeding. The blood count shows only isolated thrombocytopenia with scattered large platelets. Anemia is absent, unless there is bleeding or immune hemolysis. The bone marrow is normal except for an increase in megakaryocytes.

Pathogenesis of chronic ITP: Thrombocytopenia in ITP may be due to platelet destruction, suppressed platelet production or both. Evidence for platelet destruction: (1) infusion of ITP plasma into normal recipients may cause thrombocytopenia; (2) intravascular platelet survival is reduced; (3) autoantibody-induced platelet phagocytosis can be demonstrated and (4) ITP cytotoxic T cells can lyse autologous platelets and (5) many patients respond to therapies which affect platelet destruction, such as splenectomy, intravenous gammaglobulin (IVIg), anti-D, etc. Evidence for suppressed platelet production: (1) platelet turnover (a measure of platelet production) is either normal or reduced in over 80% of ITP patients rather than increased as would be expected if platelet destruction were the only mechanism; (2) damage to ITP megakaryocytes can be demonstrated morphologically; (3) autoantibody from some ITP patients suppresses platelet production and maturation *in vitro*; and (4) the majority of patients respond to TPO mimetics which stimulate platelet production. It is likely that ITP cytotoxic T cells

also damage megakaryocytes, since they have similar surface proteins, but this has not been confirmed.

Thrombopoietin mimetics: a new therapeutic approach: A few years ago, thrombopoietin and agents, containing the active portion of thrombopoietin, were developed and used to treat ITP patients. However, their use was discontinued when antibodies against these agents developed which rendered them inactive and, in addition, affected the function of the recipient's normal thrombopoietin. Subsequently, a variety of agents have been developed, including small peptide or non-peptide molecules, which have no sequence homology with TPO but are able to stimulate platelet production. Two of these agents, romiplostim (NPlate[®]) and eltrombopag (Promacta[®]) have undergone clinical trials and recently received FDA approval for use in chronic ITP.

Based on these clinical trials, it has been shown that both agents increase the platelet count in most chronic ITP patients most of the time resulting in reduced bleeding and allowing many patients to reduce or stop other ITP therapies. Although adverse events have been infrequent, there are potentially serious adverse events which may occur with long-term use of these agents: (1) severe thrombocytopenia upon stopping the drug with platelet counts significantly below pre-treatment levels for up to two weeks requiring, in some cases, rescue therapy; (2) increased bone marrow reticulum which thus far has been reversible in the few patients studied; (3) possible stimulation of leukemic cell growth (11 of 44 patients with myelodysplasia, receiving romiplostim, developed disease progression, four progressing to acute granulocytic leukemia); (4) hepatobiliary toxicity (eltrombopag). Potentially serious adverse events which have not been seen thus far include: thrombosis/thromboembolism, antibody formation against the drug and stem cell depletion.

Therapy of chronic ITP: Emergency therapy: Emergency therapy should be considered if the platelet count is <5000 per μ l or if there is significant mucosal or CNS bleeding. Hospitalization may be indicated. Patients should receive intravenous gammaglobulin (IVIg) 1.0 g/kg/d IV for two days and/or methylprednisolone 1.0 g/d IV for 3 days. Platelet transfusion may be indicated to control bleeding.

First-line therapy: A percentage of ITP patients will attain a spontaneous partial or complete remission if their platelet count can be maintained until this occurs. The purpose of first-line therapy is to maintain a safe platelet count (> 25–30,000 per ul) to either provide time for spontaneous recovery or to give therapy which will reverse the abnormal immune response. If no response occurs after therapy for several weeks or if patients relapse after a response, second line therapy should be given. The following therapies should be considered: (1) prednisone – 1 mg/kg daily p.o. until a response occurs followed by tapering over a period of several weeks; (2) high-dose dexamethasone – 40 mg PO or IV/d \times 4 every 14 days \times 4; (3) Anti-D – 50–75 ug/kg IV prn to maintain the platelet count >30,000 per ul; (4) rituximab – 375 mg/M² IV per week \times 4; or (5) thrombopoietin mimetics – romiplostim (1–10 ug/kg s.c. weekly) or eltrombopag (25–75 mg po daily on an empty stomach) aiming to maintain a platelet count of \geq 50,000 per ul.

Second line therapy: If there is continued, symptomatic thrombocytopenia after therapeutic trials of the above agents, there are two possible considerations: (1) splenectomy or (2) continue the thrombopoietin mimetic, if the patient continues to respond. Splenectomy would seem to be the wiser choice at this time since long-term results are not yet available for the thrombopoietin mimetics.

Splenectomy has been used for chronic ITP for over 50 years and there are solid long-term data showing that about two thirds of patients are cured of their disease. Immunizations for pneumococcus, meningococcus and H. influenza should be given and, if possible, the platelet count should be raised above 50,000 per ul pre-op using corticosteroids, IVIG or anti-D. Platelets should be available but not given unless excessive bleeding occurs. Laparoscopic splenectomy is recommended since results are equal to standard splenectomy and patients recover more rapidly and require shorter hospitalizations.

Therapy of refractory ITP: For patients failing splenectomy, several options are available. A retrial of prednisone \pm dapsone or danazol, rituximab or one of the TPO mimetics should be considered. Patients, who do not respond, can be treated with chemotherapeutic agents (azathioprine or oral cyclophosphamide) or immunosuppressants (cyclosporine or mycophenolate mofetil). In patients, who remain thrombocytopenic and have symptomatic bleeding, consideration may be given to more toxic therapy such as high-dose cyclophosphamide, combination chemotherapy or stem cell transplantation.