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Review article ■

New Frontiers of Target Therapy in Oncology: Acute Promyelocytic Leukemia

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SUMMARY

By introduction of all-trans retinoic acid (ATRA) in *de novo* acute promyelocytic leukemia (APL) an revolution in therapy of this disease has been made. The rate of molecular complete remissions (CR) have been doubled compared to conventional chemotherapy with anthracyclines ranging from 90% to 95%. Consolidation therapy is required in order to reduce the risk of early relapse. Maintenance therapy is recommended as it further reduces the risk of relapse, especially in high-risk patients. The relapse rate in APL is relatively high, about 30% and is the most common within three years of starting the treatment. Another agent, arsenic trioxide (ATO) is the optimal drug that achieves high CR rate in relapsed, approximately 80% and hematopoietic stem cell transplantation (HSCT) may prolong the overall survival in patients with APL. ATRA and ATO have become a paradigm of targeted therapy, and APL is a paradigm of curable disease, at least in comparison to other forms of acute myeloid leukemia (AML).

Key words: **acute promyelocytic leukemia, target therapy**

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INTRODUCTION

Acute promyelocytic leukemia (APL) represents a distinct clinical and pathologic entity. The unique features of APL have been well described (1, 2). It includes a characteristic morphologic appearance (3), a reciprocal translocation between the long arms of chromosomes 15 and 17 (4), younger age at onset (5), and severe consumptive coagulopathy with a high incidence of early fatal hemorrhage (1, 6, 7).

Estimated incidence accounts for approximately 10% to 15% of acute myeloid leukemia (AML) cases (1, 2). APL incidence increases steadily during the teen years, reaches a plateau during early adulthood, and remains constant until it decreases after age of 60 years (8). This is in marked contrast to other subtypes of AML. With respect to the incidence of APL among ethnic groups, contradictory data regarding a presumed higher incidence in persons from Mexico, Central and South America, Italy and Spain, have been reported in the literature (9, 10).

The introduction of *all trans* retinoic acid (ATRA), vitamin A derivatives, created a revolution in the treatment of APL. It is a paradigm of target therapy of human cancers. Cure rates of APL have been doubled compared to monotherapy with anthracyclines. Arsen-trioxide (ATO) itself is one of the most active agents against APL; it is approved for relapsed/refractory APL, and through many studies, it clears the way to first-line therapy. Gemtuzumab-ozogamicin (GO) remains an optional biological agent in patients who are not candidates for intensive treatment, or who had relapsed for several times, giving a good chance of long-term remissions.

British Committee for Standards in Hematology (BCSH), which has defined guidelines for optimal management for AML (11), recommends that centers treating 5 to 10 AML patients per year would have opportunity of treating no more than one APL patient every two years.

THERAPY APPROACH IN de novo APL

Supportive measures prior to induction therapy

There are no differences between supportive measures in APL from those appplied in other forms of acute leukemias. ATRA treatment should be initiated immediately, even if the diagnosis of APL has not been clearly verified, without waiting for genetic confirmation of the diagnosis, because early administration of ATRA reduces the risk of serious bleeding. Intracerebral and pulmonary hemorrhages are relatively common life-threatening complications occuring while the characteristic coagulopathy of APL is active. For this reason, the replacement therapy should be started immediately with administration of fresh frosen plasma, cryoprecipitate and platelet transfusion, to maintain the fibrinogen concentration and platelet count above 100 do 150 mg/dl and 30 to 50x 10^9/L, respectively, which should be monitored at least once a day. Such replacement therapy should continue during induction therapy until disappearance of all clinical and laboratory signs of coagulopathy. Patients with high risk of early fatal hemorrhage are those with: active bleeding (12), hypofibrinogenemia (<100 mg/dl) (13), increased levels of D-dimers, prolonged parcial tromboplastin time (14), WBC>10x10^9/L (15,16), high blast count in periferal blood (14, 12), high serum-creatinine (14) and poor performance status (13). In case of hyperleukocytic form of APL, the use of leukapheresis is not recommended, because of increased risk of early induction death, cosed by activated coagulopathy (17). In such situation it requires an immediate administration of ATRA and anthracycline for reduction of blast count and prevention the growth of number of WBC count under the influence of ATRA. In the aforementioned situation, a rapid development of activated coagulopathy and ATRA differentiation syndrome are threatened.

ATRA differentiation syndrome is the most common complication of the medical treatment of APL and it is characterized by the following signs and symptoms: dyspnea, fever, peripheral edema, weight gain, unexplained hypotension, acute renal failure and congestive heart failure, and by occuring of pulmonary infiltrates and pleuropericardial effusion. Syndrome is a highly life-threatening condition and it is necessery to start dexamethason 10 mg twice daily, at the very earliest signs and symptoms, temporary discontinuation of ATRA is indicated in severe clinical picture (acute respiratory distress syndrome and renal failure). There is no clear evidence that early use of corticosteroids can dicrease the risk of differentiation syndrome. In uncontrolled studies, a very low mortality or morbidity rate was reported as a result of differentiation syndrome after ATRA treatment when corticosteroids were administered prophylactically in patients presenting with WBC count greater than 5x 10^9/L (18, 19).

Treatment with ATO is associated with several electrolyte abnormalities and QT interval prolongation that can lead to torsade de pointes-ventricular tachycardia, which can be fatal (20). It is of the most importance to control the level of potassium, calcium and magnesium. ATO treatment of APL leads to hyperleukocytosis in 75% of cases, which is the most visible in a period of 20 days of the therapy initiation. The use of hydroxiurea can be considered, with regulation of WBC count in 10 days, although the clinical benefit of this treatment is unclear.

Induction therapy

Current standard approach in therapy of *de novo* APL is concomitant administration of ATRA and anthracycline-based chemotherapy. This combination results in extremely high antileukemic efficacy, leading to complete remission (CR) in 90% to 95% of patients and pri-

mary resistence has been only reported in just a few anecdotal cases (12, 15, 16, 19). Virtually, all PML-RARα positive cases of APL are sensitive to aforementioned induction regimen. ATRA in combination with chemotherapy reaches cure rates of 70% to 85% in patients with *de novo* APL. On average, about 10% of patients still die in the early phase of the tretment, mostly as a result of bleeding complications (21, 22). The concept of this therapy is defined as AIDA protocol, which has been suggested by the cooperative groups: *Programa para el Estudio de la Terapeutica en Hemopatia Maligna* -PETHEMA and *Gruppo Italiano Mallatie EMatologiche dell'Adulto*-GIMEMA.

ATRA is retionid derivative, which basic effect is in overcomming the repression signalization determined by fusion PML/RAR protein, which enables the terminal differentiation of promyelocytic-like blasts. The extraordinarily high efficacy of ATRA is APL specific (23, 24). ATRA monotherapy should be administered immediately, because the rapid control of APL specific coagulopathy is required, even in suspected cases of APL and it showed high efficacy because it led to high procentage of CR alone. Nevertheless, additional consolidation therapy is absolutely necessary to avoid the high frequency of disease relapse. Liposomal formulation of ATRA (lipo-ATRA) alone had led to durable molecular remissions in isolated small series of patients. Randomized studies of the European APL group and North American Intergroup, showed that patients receiving ATRA+chemotherapy had significantly better outcomes compared with patients treated with chemotherapy alone. In both studies, the CR and early death rates were not statistically different, but the relapse rate was significantly higher for the patients treated with chemotherapy alone (21, 24). In comparison of sequential versus concomitant (simultaneous) ATRA+chemotherapy schedule it is demonstrated that concomitant schedule had resulted in improved outcome; this was confirmed by European APL group and in other multicenter large trials, as well (15, 16, 19, 25-28). ATRA should be given immediately, continuously, over 90 days maximum period, until the achievement of hematologic remission in APL.

APL blasts are extremely sensitive to anthracyclines. The selection of anthracycline antibiotic in induction scheme did not show any clear differences between daunorubicin and idarubicin, with or without cytarabine. The results of one randomized trial showed no clear differences in a range of CR achievement when comparing ATRA+daunorubicin vs ATRA+daunorubicin+cytarabine, however an increased risk of relapse was demonstrated when cytarabine was ommited in induction and consolidation (29). In other reported randomized trial, when ATRA+idarubicin arm was compared with ATRA +daunorubicin+cytarabine, in induction, no differences were found in overall response, overall survival and relapse rate, but a small increase in deaths in remission was noted in cytarabine-containing arm (30). Idarubicin has shown a slight survival advantage compared with daunorubicin in conjunction with cytarabine only in younger AML patients (31). In APL no prospective studies have been conducted to assess the comparative value of both anthracyclines. Anthracyclines may be contraindicated in some situations (patients over 80 years, severe organ failure), or in trials where required by the study protocol. In such situations alternative agents should be used with ATRA. There are no supportive data for modification of induction protocol in high risk APL patients (Flt 3 mutation, CD56+, BCR3 or short PML-RARα isoform and secondary chromosomal aberrations).

After the introduction of ATO in the treatment of relapsed APL, several trials have been designed to investigate the role of ATO in front-line therapy. As far as we found in the literature, a few small and selected series from China, Iran, India and MD Anderson Cancer Center (Houston, TX) have been published so far, which demonstrated the rate of CR in the range of 86% to 95% (32, -35). However, it should be noted that ATO was combined with ATRA and/or chemotherapy (32, 35) and/or GO (35) in variable proportion of patients, particularly those presenting with hyperleukocytosis. APML4 trial used ATO with the standard induction remission therapy idarubicin+ATRA, in children and adults. After the induction there were two cycles more with ATO and classic maintenance therapy for two years. The results were greater in comparison with APML3 trial, where ATO was not used during induction.

General recommendation is that the use of ATO-based regimens should be restricted in cases of relapsed/refractory APL, or in clinical trials as a front-line therapy only in selected group of patients, those in whom anthracyclines are contraindicated. ATO is cheaper than ATRA, so in some countries where it is more affordable, arsenic-based regimens have been adopted as the standard of care.

The duration of induction therapy should last long enough for APL blasts to achieve maturation to granulocytes. Molecular assessment by RT-PCR confirmation of a molecular CR after the induction therapy has no clinical relevance, because PCR+ test at this early time point may reflect delayed maturation instead of resistance. Molecular remission should be assessed after consolidation. The modification of induction protocol is not required, because the resistence to this therapeutic schedule is minimal.

Consolidation therapy

After the termination of induction therapy of APL, it is of great importance to consolidate achieved CR with additional cycles of chemotherapy. The achievement of molecular remission rates of roughly 95% in patients receiving at least two futher cycles of anthracycline-based chemotherapy after induction has led to the adoption of this strategy as the standard for consolidation (36). Consolidation therapy is based upon the Sanz risk score for APL (low risk WBC$<10x10^9$/L and Plt$>40x10^9$/L, inter-

mediate risk WBC$<10x10^9$/L and Plt$<40x10^9$/L, and high risk WBC$\geq 10x10^9$/L). This scoring system serves as a significant predictor of relapse and it is used as a prognostic parameter to control the intensity of consolidation therapy (37).

Historical comparisons of consecutive trials carried out independently by the GIMEMA and PETHEMA groups showed a statistically significant improvement in outcomes whith addition of ATRA (45mg/m^2 per day for adults and 25mg/m^2 per day for children in a periode of 15 days) to consolidation therapy, and the reduction of relapse risk (19, 38).

The role of cytarabine in consolidation therapy of APL still remains controversal. Randomized trials which have compared the use of cytarabine in low-risk group of patients with ATRA+daunorubicin showed an adventage for addition of cytarabine to anthracyclines (29), however, regimens containing high dose anthracycline appear to produce as good or even better results for low -risk patients (39). For high-risk patients, a historical comparison of the LPA 2005 with PETHEMA LPA99 trial suggested that the addition of cytarabine to anthracycline+ATRA combinations can lower the relapse rate (40). The results of AIDA-2000 trial confirmed that the cumulative incidence of relapse for adult patients with high-risk disease can be reduced to approximately 10% with consolidation regimens containing ATRA, anthracycline and cytarabine (41).

The role of ATO in postremission therapy has been widely studied and demonstrated a high antileukemic activity. Two oposite options of ATO usage have been considered, first as reintensification of consolidation therapy by adding ATO to consolidation therapy and conversely, to reduce or even completely eliminate chemotherapy during induction and consolidation. US Intergroup in large randomized trial used ATO to reinforce standard ATRA plus chemotherapy regimens. In this study, patients receiving ATO in two courses of 25 days (5 days of week for 5 weeks) immediately after the patient entered a CR and before the standard postremission regimen with two more courses of ATRA+daunorubicin had significantly better event free and overall survival than those who received only ATRA plus chemotherapy (42). However, the same schedule used in pediatric patients was quite dissapointing. Iland et al. published a study which was based on the use of ATRA+ATO in induction and consolidation with limited chemotherapy exposure (anthracycline). Patients received ATRA+ATO in induction with four doses of age-adjusted idarubicin (maximum cumulative dose 48mg/m^2). Regardless of presenting WBC counts all of the patients received corticosteroid prophylactically. CR rate was 95% with an early induction death of 3.2%. Notably, it is highlighted that there were only two consolidation cycles which contained only target agents (ATRA+ ATO). All patients (n=112) achieved molecular CR by the end of consolidation and all received standard two-year maintenance regimen. Two of the 112 patients who completed consolidation and maintenance therapy relapsed, with amazing 98% disease free survival (DFS) rate in two years. Sanz risk stratification and Flt3 mutation did not affect this outcome. It is important to notice that 90% of patients could receive at least 80% of maximum total dose of ATO in both consolidations (43). This mentioned results challenges the role of cytarabine in high-risk patients as front -line therapy, and along with work by Ravandi et al., suggests that majority of APL patients may be cured with little or no chemotherapy.

Nevertheless, the exact place of ATO in consolidation, after the achievement of first remission, in the terms of number of consolidation cycles, as well in dose of ATO, remains insufficiently defined and need to be established in future prospective randomized trials.

The role of hematopoietic stem cell transplantation (HSCT) changed dramatically in the recent years. In patients who entered a molecular remission after the consolidation, the routine use of HSCT is not required. In a small fraction of patients with persistant minimal residual disease (MRD), after the consolidation, given the poor prognosis in this subset, allogeneic HSCT should be considered as an option, if they have suitable available donor (44). This particular group is at high risk of rapid progression, so ATO could be enclosed for the reduction of the disease burden and to enter the molecular CR prior to transplantation. Nearly all experiance in HSCT has been based on myeloablative regimens of conditioning, while data about reduced intensity conditioning (RIC) are currently lacking. In the group of patients who are not candidates for allogeneic HSCT, because the HLA-matched suitable donor is not available, or poor performans status, additional therapy with ATO and/or gemtuzumab ozogamicin (GO), which could bring to RT-PCR negativity of the marrow, may undergo autologous HSCT, as consolidation therapy. Although good results have been achieved using this modality (45, 46), the role of transplant is uncertain, since it is possible that long-term remissions can also be achieved with multiple courses of ATO+GO.

Maintenance therapy

Maintenance therapy in APL still remains a matter of controversy. Various studies, which have been conducted in postconsolidation therapy did not confirm clear benefit of the maintenance therapy, especially in the group of PCR negative patients after the consolidation (47). It is important to highlight that in the group of PCR negative patients, one smaller portion of them will definitely relapse, especially those with hyperleukocytic form of the disease at onset (WBC $\geq 10x10^9$/L). Some of the studies highlighted the benefit of ATRA–based maintenance therapy (15, 24), however, the molecular status has not been RT-PCR tested in this studies, so the level of residual disease was unknown. It might be that benefit was provided by the cases which were RT-PCR positive after the consolidation. Standard mainten-

ance therapy includes ATRA+6-MP+Mtx, this combination indicates an adventage over the ATRA monotherapy in randomized trials of adult patients with APL (15, 48). The benefit of the maintenance therapy mostly depends on various risk factors (risk group, the use and dose of anthracyclines during induction and consolidation, as well the intensity of previous therapies). The role of ATO maintenance of achieved remissions is controversal.

Central nervous system prophylaxis

The central nervous system (CNS) is the commonest site of extramedullary disease in APL, at least 10% of hematologic relapses are accompanied by CNS involvement (49). It is conceivable that extramedullary relapses are more apparent, given the greater availability of molecularly targeted therapies and prolonged survival in patients with APL. Some strategies suggest CNS prophylaxis for the patients with hyperleukocytosis, because this particular group of patients is in high-risk of relapse. Lumbal puncture should be delayed for the period after induction therapy, beacuse of the high risk of bleeding complications, if prefered earlier. Clear benefit of this intervention has not been established. In low-risk patients, CNS prophylaxis should not be performed.

MANAGEMENT OF SPECIFIC SITUATIONS

Elderly patients

Unlike other forms of AML arising in older patients, APL is relatively uncommon in this age group and has a relatively favorable outcome. In fact, older patients with APL seem to be responsive to therapy as younger, moreover older patients are more likely to present with low-risk features compared with younger patients (50). The relapse rate in older than 70 years of age receiving ATRA+reduced dose anthracycline is relatively low (50, 51). With PETHEMA protocol approach, mortality rate in CR ranged from less than 1% in patients younger than 60 to 19% in patients older than 70 years (50). Possible alternative in elderly could be only targeted therapy, such as ATO with or without ATRA, or eventually GO.

Children

APL accounts for 4% to 8% of pediatric AML in the US (52). Compared with the disease in adults, APL diagnosed in childhood more frequently presents with hyperleukocytosis (approximately 40% in children vs 20-25% in adults) (50). The results of long-term outcome in children by AIDA protocol are scarce, available informations are based on 4 study groups: PETHEMA, GIMEMA, German-Austrian-Swiss group and the European APL group (53, 54, 55, 56). ATRA is given in a dose of 25 mg/m^2, because of frequent side effects such as severe headache and pseudotumor cerebri. Study of Castaigne et al. (57) showed no difference in terms of pharmacokinetics, therapeutic efficacy, and side effects with ATRA 25 mg/m^2 per day compared with the standard dose of 45 mg/m^2 per day. Reduced dose intensity of anthracyclines, because of their known cardiotoxicity, have not been encouraging (42).

Pregnancy

APL in pregnanacy is a relatively rare phenomenon, but unfortunatelly possible. Available data are on the level of case report, with no evidence-based medicine in such situations. It is known that retinoids are highly teratogenic, as well ATO, and are considered contraindicated in first trimester. The abortion and then treatment or isolated use of anthracyclines are advised. There is some limited evidence that idarubicin, which is more lipophilic than other anthracyclines, favoring increased placental transfer, might be more toxic in pregnancy (58). For this reason, it has been suggested that daunorubicin might be preferred because this agent is known to be effective in APL and there is more published experience of its use in pregnancy (59). In the second and third trimester ATRA could be used sequentaly with anthracyclines. In sequental schedule ATRA is used until CR is achieved and than after birth, anthracyclines can be included. The expected response with ATRA alone is not significantly different to ATRA+ chemotherapy in terms of CR rate, but it can have an unfavorable impact of the risk of relapse (15).

Patients with severe comorbidity

Several protocols has been designed to minimize the use of chemotherapy in APL. Most of these are based on the use of ATRA, ATO and GO with minimal or no chemotherapy (35). Although there are lack of informations about long-term outcome in unfit patients by using such protocols, they simply do not have any alternative. The aim is to achieve molecular CR with MRD monitoring being used to guide the need for additional therapy.

Therapy-related APL

Therapy related APL (tAPL) demonstrates an increasing incidence after the wider use of topoisomerase II targeted drugs, in malignant and non-malignant diseases. Scarce data are available about tAPL, and they are mostly on the level of single-center experiance or case reports. The drugs most commonly implicated in tAPL are epirubicin and mitoxantrone, but several cases have been reported to follow exposure to radiotherapy alone (60-63). The occurence of tAPL is typically without preceding myelodisplastic phase and the latency period between chemotherapy exposure and onset is rela-

tively short (<3 years). Hematologic findings do not differ from those observed in *de novo* APL, except of the involvement of chromosome 5, 7 and 17, which appears to be more common than those in *de novo* APL (64). By introduction of mitoxantrone in therapy of aggressive forms of multiple sclerosis, cases of tAPL have been increasingly reported (65). Current data suggest that patients with tAPL have a relatively favorable prognosis, although the results of one study indicated a higher incidence of early death during treatment (64). Induction and consolidation therapy do not differ from those in *de novo* APL, except the limitation of anthracycline administration due to previous use in the treatment of primary process. In aforementioned situations, ATO in combination with ATRA provides an option for consolidation after standard induction therapy or as first-line treatment using schedules such as those published by the M. D. Anderson group (35).

Genetic variants in APL

In 90% of APL patients there is a classic translocation of long arm of chromosome 15 and 17. The other 10% may have variable mutations that could be resistant to the classic induction treatment. The available data is mostly based on single case reports, so there is no general recommendations based on evidence-based medicine-how to manage such situations. ATRA sensitive variants are NuMA-RARα, NPM1-RARα and FIP1L1-RARα, resistant ATRA variants are STAT5b-RARα and relatively resistant is PLZF-RARα, while PRKAR1A-RARα is of unknown sensitivity (66, 67). Sensitivity to ATO has not been documented outside PML-RARα positive APL, except for PLZF-RARα positive APL, which has been shown to be resistant (68). Generally, ATRA-sensitive variants should be treated with standard approach, while ATRA-resistant variant should be managed with AML-like approach.

RELAPSE/REFRACTORY APL

After completion of consolidation therapy in *de novo* APL, which has been introduced into CR, regular follow up monitoring is required in expectation of eventually disease relapse. The majority of relapses occurs within the first three years after completion of consolidation (69). Estimated relapse rate is about 30% and it depends on idividual risk profile (15, 19, 28, 70). Late relapses in APL are rare, and patients who maintained their CR over 5 years could be considered cured (71). Monitoring of MRD has clinical significance in APL, as the persistence or the reccurence of a positive RT-PCR of PML/RARα transcript (sensitivity $1x10^{-4}$) in hematologic remission is associated with an early relapse (72). Presently, it is quite clear that in case of relapsed APL second remission (CR2) may be achieved. The aim is to maintain the remission as long as possible. Relapsed APL can be considered through the concept of molecular, hematologic and extramedullary relapse.

Molecular relapse

Molecular relapse is subclinical (unvisible) level of disease reccurence, however, it is the introduction in massive hematologic relapse. Reccurence of PCR positivity typically is apparent first in the marrow, and occasionaly PML/RARα transcripts do not become detectable in peripheral blood until time of hematologic relapse (73, 74). PML/RARα positivity should be detected in two successive PCR tests in the span of two weeks, to avoid false positivity. Special note is needed if PML/RARα positivity, but RARα/PML negativity are detected. Such patients are not indicated for salvage treatment, however, strict monitoring of MRD is strongly recommended. Two studies carried out in the pre-ATO era have suggested a benefit for preemptive therapy in patients who develop molecular relapse compared with treatment initiated at the time of frank hematologic relapse (75). Nevertheless, concept of preemptive therapy of relapse remains to be documented in the era of proven ATO efficacy. Obvious risk of hemorrhagic death and development of ATRA differentiation syndrome in hematologic relapse in relation to molecular relapse strongly emphasizes the concept of prompt treatment of molecular relapse. The lack of specific data about optimal management for patients with documented molecular relapse leads us to assume a similar strategy to that recommended for patients with visible relapse.

Hematologic relapse

Presently, ATO is regarded as the best treatment option for relapsed APL, given it high antileukemic efficacy and relatively favorable toxicity profile (76,83). Preliminary studies with ATO as salvage therapy were carried out by the Shangai group in early 1990s (77), and then subsequently replicated in Western population. Numerous recent studies have confirmed high and sustained efficacy of ATO in relapsed/refractory APL. In those studies the rate of CR was 80% to 90%, and overall survival was 50% to 70% in a period of time from 1 to 3 years (78-82). Current evidence suggests that use of at least 2 cycles of ATO results in the achievement of second molecular CR in nearly 80% of cases (84). In a randomized trial, which included a total of 50 patients, in a comparison between ATO vs ATO+ATRA for the induction of remission in relapsed APL, no advantage was demonstrated for the combination in term of survival and relapse free survival (81). Study of a Chinese group have reported outcome in 224 APL patients (156 *de novo* APL i 56 relapsed APL), where the comparison was made between three study arms: ATO and low-dose ATRA vs ATO alone vs standard-dose ATRA alone. The results demonstrated significantly better clinical outcome in ATO

+low-dose ATRA, not only in therapeutic response, but also in reducing the ATRA-related toxic effects (85).

Optimal consolidation after second CR is unknown. According to the recommendations of Europian APL group of experts from 2007, one consolidation therapy with ATO+ATRA (ATO 0.15 mg/kg 25 days with weekend pause and concomitantly application of ATRA 45 mg/m^2 33 days), is recommended, after the arsenic induction. Patients who relapsed after ATO can enter the remission after ATO+ATRA (86). After completion of consolidation therapy, remission should be assessed by marrow RT-PCR test.

Postconsolidation therapy is optional and is a matter of a team which manages therapy. There is some evidence to suggest that treatment intensification with HSCT or chemiotherapy (may improve outcomes of patients achieving second remission with ATO (87). Selection of treatment is opened, because it depends on multiple prognostic and logistic variables (molecular status, age, duration of first CR, donor availability). In accordance with the recommendations of the European group of experts on relapsed/refractory APL, depending on the aforementioned factors, the introduction of allogeneic or autologous HSCT or chemo-targeted therapy for transplant unsuitable patients is possible.

Allogeneic HSCT could be recommended in patients failing to achieve a second molecular remission and for those with short first CR duration (84). It is an option in patients who have available suitable donor (related or unrelated-it is an open option determened by transplantional center). If RT-PCR negativity is achieved after therapy with ATO, allogeneic HSCT should be applied immediately, with no addition of conditioning regimen. In situation of RT-PCR positivity after induction and consolidation with ATO, before the allogeneic HSCT, it is necessary to intercalate high-dose regimen HAM (high doses of cytarabine 3g/m^2+mitoxantrone 10mg/m^2) in patients <60 years, or reduced intensity HAM (cytarabine 1 g/m^2) in patients >60 years, in order to achieve negative RT-PCR, and than to apply allogeneic HSCT.

Autologous HSCT is preferable in situations if the first CR lasted for more than one year and if relapse is sensitive (second molecular CR is attainable). It is an option in situations when there is no eligible donor for allogeneic HSCT, and is also followed by less complications and lower mortality associated with the procedure. RT-PCR negative cases, after consolidation with ATO, are indicated for autologous HSCT. As mobilization protocol only granulocytic colony stimulating factor (G-CSF) or low-dose chemotherapy and than autologous HSCT could be used. In case of RT-PCR positivity, it is indispensable to apply high dose regimen HAM, to achieve negative PCR test. If APL is refractory to this protocol auto HSCT is not indicated any more, rather allogeneic HSCT or post-consolidation chemo-targeted therapy, if donor is not available.

Both autologous and allogeneic HSCT are connected with durable remissions and extended overall survival in APL patients. In a retrospective analysis, overall survival for patients who underwent transplant was not significantly better than those who received only chemotherapy, but the trend of slightly better outcome was noted in the group with autologous HSCT, although not statistically significant (88).

In patients not fit for HSCT, or refractory, the available options include repeated cycles of ATO with or without ATRA+standard chemotherapy. Anti CD33 monoclonal antibody GO, conjugated with calicheamicin, in one monthly dose of 6 mg/m^2, appears to induce a high rate of durable molecular remissions, even as a single agent in advanced disease (89). Takeshita et al. reported activity of GO on ATRA and ATO resistant APL cell lines (90). Optional salvage combinations are the combinations of ATO+ATRA+GO, or ATRA+Metotrexate+6-MP or intensive chemotherapy protocol HAM±ATRA.

Extramedullary relapse

Extramedullary relapse can be synchronous or asynchronous with the involvement of bone marrow with leukemia. At least 1 in 10 patient will have CNS ivolvement, therefore this site should be particularly considered in molecular or in hematologic relapse (49, 91, 92). Relapse in the CNS is partly due to the long survival of these patients, which was not the case before. Optimal managament in such situations have not been critically assessed, so it seems pragmatic to pursue an approach derived from experiances of the management of extramedullary relapses in acute lymphoblastic leukemia (ALL) and other subtypes of AML. Therefore, CNS relapse need to be treated with application of triple intrathecal therapy (ITT), with cytarabine, metotrexate and hydrocortisone in weekly intervals until complete clearance of blasts from cerebro-spinal fluid, followed by 6 to 10 more spaced out ITT treatments as consolidation. Occurence of CNS involvement is almost invariably accompanied by hematologic or molecular relapse in the marrow, so systemic treatment should also be given. One approach could be the application of targeted agents ATRA and ATO, as non-myeloablative treatment with ITT. In responsive extramedullary relapse, chemotherapy regimens with high CNS penetrance (high dose cytarabine) can be used, allogeneic or autologous HSCT should be the consolidation treatment of choice including appropriate craniospinal irradiation. In case of granulocytic sarcoma, wherever it is localized, radiation and intensive systemic therapy should be applied.

CONCLUSION

In the last two decades, the advent of two new agents (ATRA, ATO) as a target therapy in APL completely reversed the course of treatment of this serious disease. APL has gone from one of the most deadly disease, to date, to one of potentially most curable acute leukemia. ATRA is an example of inteligent therapy that emphasi-

zes differentiation of blasts and their apoptosis, while anthracyclines still persist as a primitive part of therapy, but still as standard of cure. ATO as an old-new drug, which is highly effective in relapsed APL slightly clears a way to front-line therapy, and in some categories of patients it removes the use of conventional chemotherapy of the focus of treatment, positioning the isolated use of targeted therapy only. ATRA is presently a paradigm of targeted therapy in oncology, as cited many times, and APL slightly becomes a paradigm of curable disease, at least in comparison to other forms of AML.

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NOVI VIDICI CILJANE TERAPIJE U ONKOLOGIJI: AKUTNA PROMIJELOCITNA LEUKEMIJA

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Sažetak

Uvođenjem all-trans retinoične kiseline (ATRA) u *de novo* akutnoj promijelocitnoj leukemiji (APL) napravljena je revolucija u terapiji ove bolesti. Stopa molekularnih kompletnih remisija (CR) udvostručila se u odnosu na konvencionalnu hemioterapiju antraciklinima i kreće se 90-95%. Konsolidaciona terapija je obavezna radi redukcije rizika od ranog relapsa bolesti. Terapija održavanja je preporučena jer dodatno redukuje rizik od relapsa, pogotovo kod visoko rizičnih bolesnika. Stopa relapsa APL je relativno visoka, oko 30%, i najčešća je unutar tri godine od početka lečenja. Drugi agens, arsen trioksid (ATO) je optimalni medikament koji postiže visoke stope CR u relapsu, oko 80%, a transplantacija matičnih ćelija hematopoeze (TMĆH) može produžiti ukupno preživljavanje bolesnika sa APL. ATRA i ATO su postali paradigma target terapije, a APL paradigma kurabilne maligne bolesti, bar u odnosu na druge forme akutnih mijeloidnih leukemija (AML).

Ključne reči: **akutna promijelocitna leukemija, ciljana terapija**