Case reports

Rapid Efficacy of Gemtuzumab Ozogamicin in Refractory AML Patients with Organ Dysfunctions

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Abstract: Objectives: To demonstrate the efficacy of Gemtuzumab ozogamicin in refractory AML patients with organ dysfunctions and poor performance status.

Three refractory AML patients with are described. One of them was pretreated by intensive chemotherapy, two other patients progressed during Azacitidine treatment. WHO performance status III . Two patients had respiratory failure grade 2, the other one suffered from acute kidney insufficiency. Two patients were highly febrile with elevated CRP level.

Gemtuzumab ozogamicin administration was performed in three patients followed by further switch to Gemtuzumab ozogamicin + Azacitidine or "7+3" treatment. Results: Gemtuzumab ozogamicin administration resulted in abrupt fever cessation in two febrile patients simultaneously with CRP level decrease and fast gradual resolution of respiratory failure. Recovery of kidney function was noticed in patient with renal insufficiency. WHO performance status have elevated in all three patients. No adverse effects grade II-III were noticed. Further treatment made two patients eligible for intensive chemotherapy, one patient was transplanted, patient with kidney failure obtained complete remission. Conclusions: Gemtuzumab ozogamicin therapy appeared to be safe and highly efficacious in relapsed/refractory AML patients with organ dysfunctions and poor performance status.

Keywords: acute myeloid leukemia; patients with organ dysfunction; gemtuzumab ozogamicin

1. Introduction

Patients with acute myeloid leukemia (AML) comprise the cohort of patients at a higher risk for life-threatening complications and ICU admission for intensive monitoring and treatment due to the severity of the disease, hospital-acquired infections and intensive chemotherapy regimens used. [1,2].

Relapsed and refractory AML (10-40% of AML) represents the most common group of AML patients with organ dysfunctions and poor outcomes [3].

Early ICU admission improves survival and may be appropriate in patients with incipient organ dysfunction [2], including patients with kidney dysfunction for acute kidney injury prevention[4].

Moreover, cancer chemotherapy along with life-sustaining therapies in critically ill patients with cancer-related organ dysfunctions is feasible and associated with a meaningful survival benefit in selected patients [4].

The most common complication of refractory AML salvage therapy is pneumonia caused by different infectious agents[5].

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Thorough examination of pulmonary infiltrates occuring during treatment some uncertainties regarding their origin still remain [6].

Approximately 34-40% occurred during the disease and treatment are of infectious origin, 34% are noninfectious, and in 24% the cause [6]. Lung infiltrates is also described [7,8].

Hypoxemic acute respiratory failure with pulmonary infiltrates is one of the major life-threatening complications in patients with hematological malignancies. Management of these patients is complex, and is associated with poor outcomes [4].

Furthermore, sepsis also remains to be one of the independent prognostic risk factor for patients death [9]. Recent studies have revealed sepsis is an extremely complicated immunopathological process [10], and it has been shown that Il-6 blockade can prevent inflammatory-induced organ damage [11]. This direction could become a promising approach to sepsis therapy.

Major concerns related to administration of chemotherapy in the ICU lie in the practical issue of team experience [4]. In our opinion, patients with organ dysfunctions deserve special attention and a searching for non-toxic chemotherapy regimens.

Low toxicity of Gemtuzumab ozogamicin (GO) seems to provide a new promising option for highly compromised patients treatment. Amadori et al. reported the results of GIMEMA trial of GO versus best supportive care in the treatment of unfit for intensive chemotherapy patients in a front-line setting [12]. The toxicity of GO was comparable to best supportive care, whereas statistically significant increase of overall survival was shown in the GO arm. Moreover, GO has been shown to be an efficacious treatment in relapse/refractory AML patients [13,14]. However, significant organ dysfunctions were the exlusion criteria in these trials. To the best of our knowledge, data of GO use AML patients with organ function are lacking.

Here, we describe three patient with organ failures benefited from GO use. All of them had uncontrolled leukemic overgrowth.

2. Clinical cases

Three male patients with refractory CD 33+ AML, who had had organ dysfunction and poor WHO status performance at the moment of the therapy initiation, have been included in our clinical observation.

Clinical data and the results of the therapy of patient G.A. is presented below. Clinical data and results of the therapy of patients A.D. and L.Ja. are summarised in table 1 (see table 1)

35-year-old male patient with primary chemorefractory acute myeloid leukemia with maturation, intermediate risk group ELN2017 . Bone marrow was hypercellular with 33,5 % of blast cells. Cytogenetic analysis revealed a trisomy 8. No molecular abnormalities were detected .

Two induction cycles of «7+3» regimen without remission were followed by therapy in "FLAG" regimen. The latter therapy was complicated with a febrile neutropenia, the bloodstream infection associated with Ralstonia pickettii and polyresistant Klebsiella pneumoniae, an activation of CMV infection. Antibacterial medications according to in vitro sensitivity and empirical animycotic therapy was started on day 8 of "FLAG". Gancyclovir was added on day 9 of "FLAG". Four consecutive switches of antibacterial therapy and two switches of antifungal therapy were made. The latest modification of antifungal therapy was made on day 13 and antibacterial therapy on the following day. During all the period of antibacterial/antifungal therapy the patient condition continued to get worse. The patient had experienced high fever, CRP increased up to 295 mg/l (Fig. 1). WHO performance status of 3 had been assessed. Eventually, the patient had progressed to acute respiratory failure grade 2 with progressive increasing of dyspnea and worsened isolated hypoxemia (Fig. 1).

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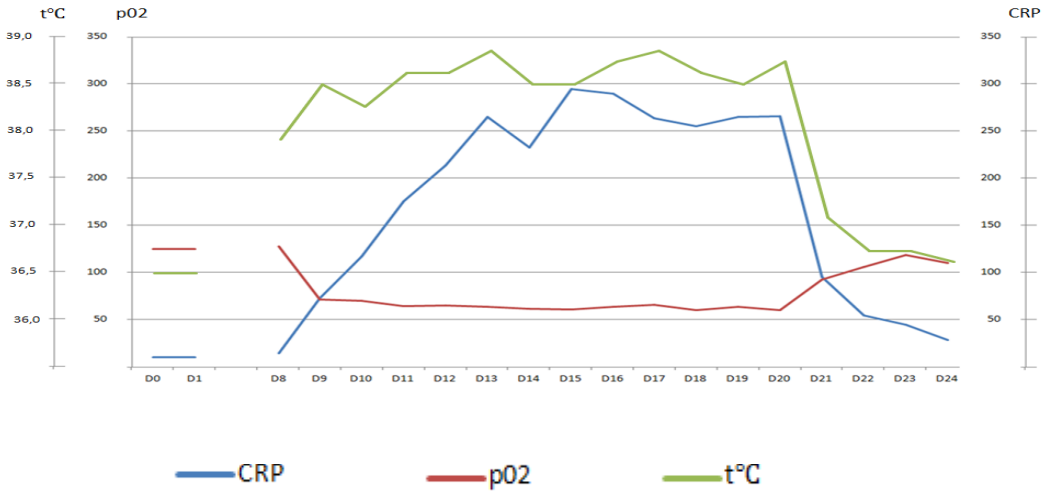
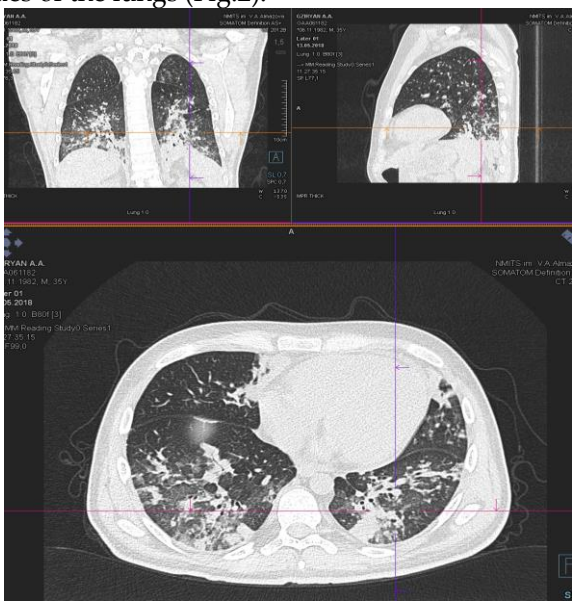


(CRP, PO2, temperature before «GO")

Figure 1.

Increaseing in size lung infiltrates were revealed on serial CT scans.

A chest CT scan on day 18 of "FLAG" showed massive infiltrates in the basal segments of the lower lobes in both lung fields with dense peribronchial lesions, multiple small interstitial lesions in S1, S2-3, S6, S8 on both sides of the lungs (Fig.2).



(CT chest scan on day 18 of "FLAG")

Figure 2.

Repeated broncho-alveolar lavages ware negative for any pathogens, galactomannan was negative.

Marrow blast cells reached 91.6% with 62.2% of CD33 positive cells on day 19 of "FLAG".

GO therapy was started on day 20 of "FLAG" therapy (Day I of GO).

During Day I after GO administration blood gas normalization with acute respiratory failure recovery was achieved. Apyrexia was noticed on Day II after GO infusion (fig.3).

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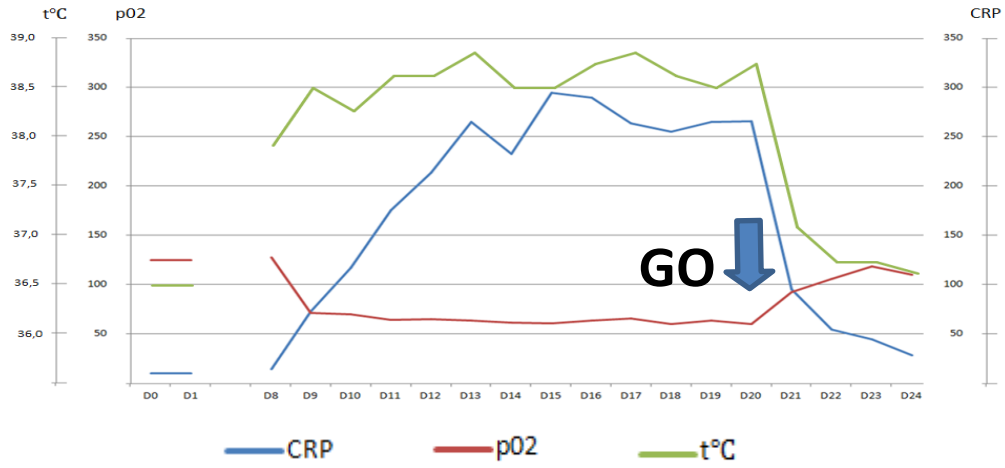
CRP started to decline and fell down to 29 mg/l on Day V after Gem. (Fig.3).



(CRP, PO2, temperature after «GO")

Figure 3.

WHO performance status improved to 2 grade.

A chest CT scan on Day III of the GO therapy showed a significant regression of pulmonary infiltrates in the size and density (Fig.4).

(CT chest scan on day III of "GO")

Figure 4.

Therapy was augmented by «Gemtuzumab ozogamicin+Azacitidine» regimen (GO 3mg/m2 day 8, Azacitidine 50mg/m2 days 1-7), which was started on Day V after GO. The patient was treated by the two consecutive cycles of the therapy in "Gemtuzumab ozogamicin+Azacitidine» regimen. No non-hematological adverse effects grade 3-4 were observed. Antibacterial therapy was

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gradually deescalated and stopped. Marrow blast cells count in the marrow gradually decreased. Best response after the 2nd cycle of the therapy was morphologic free leukemia state (MLFS)achievement: blasts count 1,5% without peripheral blood cells recovery (not shown)

The patient underwent allogeneic stem cell transplantation from a matched related donor with complete remission with complete donor chimerism achievement (not shown).

Table 1. Clinical data and results of the therapy of patients A.D. and L.Ja. are summarised in the table

Sex **Age**	**Male patient. 74 years** **A.D.**	**Male patient. 54 years** **L.Ja**
Diagnosis	AML without maturation (NOS, WHO2016). Intermediate risk group (ELN2017). Normal karyotype. Primary refractory disease.	AML with maturation (NOS, WHO2016). add(21)(q22). Intermediate risk group (ELN2017). Primary refractory disease.
Clinical data	A patient with a progression disease during the treatment by Azacitidine. Increasing blast cells in blood and marrow more than by 50% from baseline after 2 cycles of Azacytidine therapy.	A patient with a progression disease during the treatment by Azacitidine. Increasing blast cells in blood and marrow more than by 50% from baseline after 2 cycles of Azacytidine therapy.
Patient status before Gemtuzumab ozogamicine therapy initiation	WHO status performance of 3. Marrow blast cells 88,6%, peripheral blood blast cells 60%, pancytopenia grade 3-4. CRP was slightly increased to 20 mg/l. Acute kidney failure grade 2 with no prior history of chronic kidney disease or the use of a nephrotoxic agents. Creatinine increasing up to 2,8xULN and GFR decline to 15 ml/min.	WHO status performance of 3. Marrow blasts cells 68% . High fever and elevated CRP level up to 332 mg/l with no response to escalated antibiotics/antimycotics combination. The patient had respiratory failure grade 2 with massive bilateral polysegmental lungs infiltrates according to a chest CT scan.
Regimen of therapy with GO	«GO » 1 cycle «GO+Aza» 1 cycle	«GO » 1 cycle
Response to the therapy	WHO status performance improved to grade 2. Kidney function began to improve immediately after GO infusion. Creatinine started to decrease on day 1 of the therapy and returned to normal value on day 6 (GFR elevated up to 72ml/min on day 6). Thus recovery after acute kidney injury occurred on day 6. There were blast clearence in peripheral blood on day 5 after GO therapy. On day 5 after GO infusion «GO+Aza» therapy was initiated. No any laboratory signs of kidney injury were noticed during all period of the therapy in the «GO+Aza» regimen.	WHO status performance improved to grade 2. Apyrexia was achieved on day 3 of the GO therapy CRP level started to drop on day 1 of the therapy (CRP on day 2 – 250mg/l, on day 7 – 60mg/l) A chest CT scan on the 6th day of the GO therapy showed a significant regression of pulmonary infiltrates in the size. Day 7 marrow blast cells 46%. Thus blast cells reduction was achieved on day 7 after GO infusion. The patient became eligible for chemo intesification. On day 12 of the therapy "7+3" was initiated

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	Day 14 marrow blast cells 16,1%. Peripheral blood cells recovery was achieved on day 40 of the «GO+Aza» therapy. Day 40 the marrow blast cell 1%. Thus complete remission with peripheral blood cells recovery was achieved.	

3. Discussion

In three patients with a primary resistance to standard chemotherapy regimens ("FLAG" or Azacitidine), poor performance status and organ dysfunctions (respiratory failure, acute kidney injury) GO monotherapy was chosen for the treatment. CD33blast cell positivity was obligatory for including the patients in this treatment plan.

All the patients had leukemia progression. Patients(G.A., L. Ja.) with respiratory dysfunction were resistant to preceding and ongoing antimicrobial and antiviral therapy.

They had persistent fever, increased CRP level, bilateral polysegmental lungs infiltrates with symptoms of acute respiratory failure.

Following GO administration their arterial blood gases gradually improved over the first days (patient G.A. on day I, patient L. Ja. on day II) . Apyrexia was achieved over the first three days after GO (patient G.A. on day II, patient L. Ja. on day III). CRP value started to decrease dramatically over the first day after GO infusion and continued to decline progressively. A repeated chest CT (In patient G.A. on day III, in patient L. Ja. on day VI) showed a partial regression of infiltrates after the therapy.

Patient L. Ja. became eligible for chemo intesification and was switched to "7+3" regimen with insignificant bone marrow blast cell reduction (48% blast cells)

In patient with acute kidney injury (A.D.)with no prior history of chronic kidney disease, use of nephrotoxic agents or tumor lysis syndrome signs, creatinine started to decrease on day I after GO and returned to normal value on day VI.

Therefore, a rapid resolution of renal insufficiency on GO therapy (patient A.D.) as well as drastic decrease of infiltrative lung lesions (Patients G.A. and L. Ja.) could be presumably attributed to anti-leukemic effect this medication. the overall incidence of extramedullary lesions reported in the literature ranging from 2.5% to 30% [15].

However, due to thrombocytopenia grade 4 with refractoriness to platelets transfusion organ biopsy was not performed in all three patients.

At the next step, patients G.A. and L. Ja. were switched to combined Gemtuzumab ozogamicin treatment due to the ability of the latter to potentiate the efficacy of GO and overcome resistance to GO [14, 16]. After two cycles of this regimen, morphologic free leukemia state was achieved in patient G.A. and complete remission with peripheral blood cells recovery in patient A.D..

As it is the response to mono GO or in combination with Azacitidine has been previously described in R/R AML patients even with extramedullary involvements (17,18,19), although, nobody report the immediate response to Gem. Nevertheless, Mechanism of GO pharmacokinetics provides explanation for this prompt effect. GO rapidly binds to its receptor followed by immediate internalization of cytostac-antibody complex leading to apoptosis of CD33 positive leukemia [20]

The alternative explanation of the rapid response to the GO therapy could result from its significant immunomodulatory effect.

In a xenomodel of macrophage activation syndrome GO was able to resolve symptoms and led to complete recovery of experimental animals [11]. Pathogenetic mechanisms of sepsis and macrophage activation syndrome are close [21].Possibly, rapid positive efficacy of GO in our patients arises from its ability to decline the levels of proinflammatory cytokines, thus ameliorating clinical and laboratory signs of tissue damage. Of interest, incidence of grade Grade 3 or 4 sepsis (17%) and pneumonia (8%) was lower than expected in relapsed AML CD33 positive patients [22].

The annoying limitation of our case report descriptions is a lack of cytokines level data and morphological assessment of organ lesions.

Nevertheless, we suggest our clinical experience deserves attention of hematologists/oncologist.

5. Conclusions

We have made a successful attempt to treat three severally ill patients with organ dysfunction by GO. In all of them patients, organ failure (respiratory failure and acute kidney injury) resolution was achieved after a single GO infusion. Therefore, the patients became fit to the further therapy ("7+3", "Gemtuzumab ozogamicin+Azacitidine"). No additional hematological and non-hematological toxicity was noticed.

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