Clinical Research Paper

Efficacy of GDP regimen (gemcitabine, dexamethasone and cisplatin) on relapsed or refractory aggressive non-Hodgkin’s lymphoma

A report of 24 cases

Yun Fan,* Zhi-Yu Huang, Lu-Hong Luo, Hai-Feng Yu

Department of Chemotherapy; Zhejiang Provincial Tumor Hospital; Hangzhou, Zhejiang P.R. China

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Background and Objective: The prognosis of relapsed or refractory aggressive non-Hodgkin’s lymphoma (NHL) after front-line therapy remains poor. The development of more effective and less toxic salvage regimens remains a major challenge. Gemcitabine is effective in treating lymphoma and, when combined with cisplatin, is effective for some solid tumors. This study was to evaluate the efficacy of GDP regimen (gemcitabine, dexamethasone and cisplatin) on relapsed or refractory aggressive NHL, and observe the adverse events. Methods: Patients with relapsed or refractory aggressive NHL, measurable disease who had previously received at least one chemotherapy regimen were enrolled and treated with GDP regimen (gemcitabine 1,000 mg/m² on days one and eight, dexamethasone 20–40 mg on days 1–3, and cisplatin 25 mg/m² on Days 1–3) every three weeks. The efficacy and adverse events were evaluated according to the WHO criteria. Results: Twenty-four patients received a total of 76 chemotherapy cycles and were assessable for efficacy and adverse events. Five (20.8%) patients had complete response, nine had partial response, eight had stable disease, and two had progressive disease. The overall response rate (RR) was 58.3% for assessable patients; it was 57.1% for B-cell NHL patients and 60.0% for T-cell NHL patients (p = 0.889). The median follow-up was 1.2 years. The one-year overall survival rate was 41.7%; it was 42.9% in B-cell NHL patients and 40.0% in T-cell NHL patients (p = 0.986). The occurrence rate was 37.5% for grade III/IV leucopenia, 25.0% for trombocytopenia, and 16.7% for anemia in all patients. Non-hematologic toxicities were mild. There was no treatment-related death. Two patients proceeded to stem cell transplantation after salvage chemotherapy and obtained sufficient stem cells. Conclusion: GDP regimen is an effective and relatively nontoxic salvage chemotherapy regimen for relapsed or refractory aggressive NHL.

Chemotherapy with primary use of anthracycline, such as CHOP, is still the first-line treatment in dealing with invasive non-Hodgkin’s lymphoma (NHL). Although the clinical practice of monoclonal antibodies of Rituximab boosts the curative rate for NHL of B-cells, there are still reports of 50–60% of patients with invasive NHL experiencing drug tolerance and recurrence after the first-line treatment. An effective contingency plan with low toxicity remains an objective for research by clinical practitioners. Gemcitabine is a derivative of cytidine with a structure similar to cytosine arabinoside. Research shows that Gemcitabine has anti-tumor activities against leukemia and lymphoma. Previous research proves that Gemcitabine has a synergic enhancing effect with Cisplatin (DDP). The combination of the two yields a better therapeutic effect on solid tumors. Other foreign reports show that the GDP proposal, which is composed of a combination of Gemcitabine, Cisplatin (DDP), and Dexamethasone, reaches an effective rate as high as 49% for treating recurrence and drug tolerance in invasive NHL, as well as 16% of complete remission rate. In order to assess the therapeutic effect and toxicity reaction to the GDP proposal in treating recurrent and drug tolerant invasive NHL in China, we conducted this.

Data and Methods

Clinical data. Twenty-four cases of recurrent or drug-tolerant invasive NHL admitted and treated by the tumor hospitals in Zhejiang province during the time period from January 2003 to October 2006 were collected for study. All cases satisfied the following criteria: confirmation by histopathological examination, existence of measurable lesion, complete systemic assessment (ECOG) grades zero to two, expected survival time of greater than six months, age ≤75, >18 peripheral white blood
cell count >3.5 x 10^9/L, platelet count >100 x 10^9, and normal hepatic and kidney functions.

The ages of these 24 patients ranged between 20 and 72, with a median age of 52. Eight females and 16 males were studied. As for the PS grade, there were 20 cases with grade zero to one and four cases with grade two. Clinical staging was based on the Cotswald staging method proposed in 1991. There were seven cases in phase I-II and 17 cases in phase III-IV. In the level of lactose dehydrogenase (LDH), 11 cases were normal and 13 cases had higher levels of LDH. Five cases showed type-B symptoms. International prognostic index (IPI) showed: six cases with grade zero to one, eight cases with grade two, nine cases with grade three and one case with grade four to five. As for the pathological types, there were nine cases of diffuse large B-cell lymphoma, five cases of peripheral T-cell lymphoma with unspecified type, two cases of mantle cell lymphoma, two cases of NK/T-cell lymphoma, one case of intestinal T-cell lymphoma, one case of precursor T-lymphoblastic lymphoma, one case of anaplastic large cell lymphoma, one case of T-rich B-cell lymphoma and two cases of unclassified B-cell lymphoma. Fourteen cases were of B-cell origin and ten were of T-cell origin. Ten patients experienced infiltration outside lymph nodes; four cases experienced more than two spots of infiltration outside lymph nodes. There were two cases of infiltration to bone marrow and six cases suffered enlarged spleen or infiltration.

All patients received at least one chemotherapeutic proposal and the first-line treatment is CHOP, CHOEP, or a proposal similar to CHOP. The digit of used chemotherapy was two (1–4), where the medium therapeutic number was six (2–10). Twenty patients showed recurrence after remission (PR) or complete remission (CR).

Treatment proposal. GDP proposal included: intravenous injection of 1,000 mg/m^2 Gemcitabine with 250 ml saline solution, d1, 8; intravenous injection of 25 mg/m^2 DDP with 500 ml saline solution, d1-3; and intravenous injection of 20–40 mg DXM with 100 ml saline solution, d1-3. One repetition per three weeks was considered a cycle. For patients showing effectiveness in contingency chemotheraphy and his or her economic condition permitted, the patient should have autonomous stem cell transplantation. Two patients received autonomous stem cell transplantation after they had complete remission (CR) after GDP therapy and the pre-treatment used was BEAM. If peripheral white blood cell count was lower than 2.0 x 10^9/L or the neutrophil count was lower than 1.0 x 10^9/L during the chemotherapeutic period, then G-CSF therapy was administered. If adverse reaction of IV-degree showed, then the chemotherapeutic drug dosage was reduced by 15–25% on the next run. Before each therapeutic run, the absolute value of neutrophil was greater than 1.5 x 10^9/L and the platelet count was greater than 90 x 10^9/L, while there was no non-hematological toxicity of III and IV-degree. If the standard above was not met, the next run was postponed until the standard was satisfied.

Standard for assessing therapeutic effect and toxic response. The assessment for therapeutic effect would be based on the assessment standard for therapeutic effect on solid tumors set by WHO in 1981, in which it was classified into CR, PR, stable disease (SD), progressive disease (PD), and overall response rate (ORR = CR + PR). Based on the acute and sub-acute grading standard for anti-tumor drugs set by WHO in 1981, the toxic response was graded from 0 to IV degrees.

Statistical analysis. SPSS 10.0 software was used to enter these data for statistical analysis.

Results

Short-term effect. Each patient received at least two cycles of chemotherapy, with a total of 76 cycles of chemotherapy. In 24 patients, five received two cycles, ten received three cycles and nine received four cycles. In 76 cycles, there were ten cycles with reduction in dosage (13.2%) for five patients. In 76 cycles, there were 20 cycles with delay in drug administration (26.3%) for eight patients. Four dosage reduction patients and seven delayed drug administration patients did so because of bone marrow inhibition.

All 24 patients could be assessed for therapeutic effects: Five cases of CR, nine cases of PR, eight cases of SD and two cases of PD. 58.3% had ORR and 20.8% had CR. The ORRs for B-cell NHL and T-cell NHL were 57.1% (8/14) and 60.0% (6/10), respectively. There was no statistical significance between the two (p = 0.889).

Survival rates of all patients. Follow-ups continued until June 2007, with a medium follow-up time of 1.2 years. One-year survival rate of all patients was 41.7% (10/24) and the one-year survival rates for B-cell NHL and T-cell NHL were 42.9% (6/14) and 40.0% (4/10), respectively. There was no statistical significance between the two (p = 0.986).

Toxic adverse reactions. All 24 cases could be assessed for toxic reactions; the primary one was bone marrow inhibition. Hematological toxic reactions: four patients (16.7%) showed reduction in hemoglobin of III-IV degrees and these four patients (9.2%) required perfusion of red blood cells in seven cycles; nine patients (37.5%) showed reduction in white blood cells of III-IV degrees; five patients (20.8%) showed fever of reduced granocytes; six patients (25.0%) showed reduction in platelets of III-IV degrees and three of them (6.6%) required perfusion of platelets in five cycles; thre was no report of hemorrhage. Non-hematological toxic reactions were mostly restrained to I and II degrees and the most common response was the digestive reaction. The incidence rates of nausea of III and IV degrees were seven cases (29.1%) and five cases (20.8%), respectively. Four cases showed hepatic toxicity of I-II degrees (16.7%), while one (4.1%) showed hepatic toxicity of III degree. Seven patients (29.2%) showed toxicity to peripheral nerves of I-II degrees, while no report of toxicity to heart and kidney of III-IV degrees was seen. Because 17 patients had deep vein catherization, the incidence rate for phlebitis was low. In two patients who had autonomous stem cell transplantation, the effect of transplantation was not influenced by chemotherapy. The amount of CD34 positive cells isolated per trial was more than 2.0 x 10^6/kg. No report of mortality related to treatment was seen.

Discussion

Research showed that the overall effect rate, the rate of complete remission, and the one-year survival rate for GDP proposal in
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For recurrent and drug tolerant invasive lymphoma, the contingency of a large quantity of chemotherapy with sequential treatment by stem cells can indeed cure some patients, and this has become the choice for young patients who are sensitive to chemotherapy. Lowering the overload of lymphoma and searching for an effective contingency plan with low toxicity have become the biggest challenges. An ideal contingency plan should have a higher remission rate and acceptable toxic responses while not injuring the motivation capability of peripheral stem cells. Many current contingency plans, such as DHAP, ICE, ESHAP and etc., primarily include using of the following: a large dosage of cytosine arabinoside, DDP, Cisplatin and a large dosage of steroids. The efficacy rates of these proposals are between 39–69%, but patients usually need to be admitted for treatment for corresponding toxic responses. Because of accumulated toxicity to bone marrow, the motivation capability of peripheral stem cells can be affected. Gemcitabine is a derivative of cytidine and even though it has a structure similar to cytosine arabinoside, it can be more quickly absorbed by cells, more effectively phosphorylated and stays in cells for a longer period of time. Because it also has autonomous enhancing capability, Gemcitabine can accumulate and increase in lymphoma tumor cells and stay in them longer. By inhibiting DNA synthesis through preventing the activity of ribonucleotide reductase, the concentration of intracellular nucleotide pool is reduced. These advantages allow Gemcitabine to have more anti-tumor activities when compared to higher dosage of cytosine arabinoside, while it also has lighter inhibition on bone marrow. Fossa et al. reported that a single use of Gemcitabine in 31 cases of recurrent and drug-tolerant invasive lymphoma yielded six effective cases, 11 stable cases and 19% ORR. The medium non-progressive time in effective patients was six months with a light degree of toxic responses. This study provided the basis for the combinational use of drugs with Gemcitabine in treating malignant lymphoma. The National Tumor Research Center in Canada reported the Phase II study results of GDP therapy for recurrent and drug-tolerant invasive lymphoma. In 41 cases, after two cycles of chemotherapy, the ORR reached 49% and CR reached 16%. After the completion of all planned treatments, the ORR was 53%, and 22 patients successfully received stem cell transplantation and its motivating capability was not affected, while the toxic responses could still be tolerated and the chemotherapy was done in the out patient department. Shu-Dong Ma et al. reported that the combination of Gemcitabine, DDP and DXM for treating 15 cases of recurrent and drug-tolerant invasive NHL resulted in a good conclusion of 73.3% ORR and 33.3% CR. In the treatment of intractable peripheral T-cell lymphoma, the combination of Gemcitabine, DDP and methyldeoxamethasone demonstrated a breakthrough—the remission rate reached 69%. The research demonstrated that the overall effective rate, CR, and the one-year survival rate for GDP therapy in treating recurrent and drug-tolerant invasive NHL were 58.3%, 20.8% and 41.7%, respectively. The ORRs for T-cell NHL and B-cell NHL were 60.0% and 57.1%, respectively, while no statistical significance was seen between the two. When comparing the study with our reported research results on MINE therapy for recurrent and drug-tolerant invasive NHL (ORR 41.4%, CR 15.8% and ORR of T-cell lymphoma 25.0%), the overall remission rate was improved, especially the remission rate for T-cell lymphoma. Further random controlled studies should be done to understand whether GDP therapy is better for treating T-cell lymphoma.

When selecting an appropriate contingency plan for malignant lymphoma, the factor of its toxicity to bone marrow should be considered, as it may injure the stem cells in bone marrow and affect the later motivation of these stem cells. For the patients of the group with inhibition on bone marrow, the incidence rates of reduction in white blood cell count of III-IV degrees and reduction in platelets were 37.5% and 25.0%, respectively. 20.8% showed fever of reduced granulocytes. 9.2% of cycles required perfusion of red blood cells and 6.6% of cycles required perfusion of platelets. According to reports, in ICE therapy and BEAM therapy, the ratios for perfusion of red blood cells were 35% and 60%, respectively, while the ratios for perfusion of platelets were 16.5% and 78.0%, respectively. In comparison to these common therapies, the bone marrow inhibition in GDP therapy was relatively lighter, and thus, it had an advantage in the aspect of toxic response. In this study, the non-hematological toxic reactions were mostly I-II degrees. One case showed III-degree hepatic toxicity, in which the patient recovered well after liver treatment. In the two patients who underwent stem cell transplantation, the motivating capability of stem cells was not affected by contingency plan.

Overall, GDP therapy is an effective contingency plan with relatively low toxicity for treating recurrent and drug-tolerant invasive NHL. It can be done in the outpatient department and does not affect the required stem-cell activation in transplantation. Whether it is effective for recurrent and drug-tolerant T-cell lymphoma requires further study. More multi-center, random, controlled studies must be done to understand the effect and toxicity to other commonly used second-line treatments.

References

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