· 临床病理讨论 ·

Clinicopathological Conference

An elderly patient with refractory and recurrent acute myelomonocytic leukemia treated with haploid HLA-matched cytokine-induced killers

(the 32nd case)

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Case report

A 65-year-old man was admitted on October 23, 2007 because of intermittent swelling and pain of gum and rhinorrhagia for 3 months. Three months ago, he got the above symptoms and presented to Xiangya Hospital affiliated to Zhongnan University. Laboratory tests showed: hemoglobin (Hb) 75g/L; white blood cells 28.1×10^9/L with significant increase in of abnormal blast cells; platelet, 21×10^9/L. Bone marrow examination showed that primitive and naïve monocytes accounted for 49% of nucleated cells. The diagnosis of acute myelomonocytic leukemia (M4b subtype) was made. He successively received two cycles of standard chemotherapy with the first regimen of IA (idamycin + cytarabine) and the second regimen of HA (homoharringtonine+cytarabine), but remission was not achieved. Salvage chemotherapy with AMA regimen (arsenous acid+mitoxantrone+cytarabine) was given. End time of chemotherapy before admission was October 12, 2007. He was a smoker for 40 years with 20 cigarettes a day.

On admission, physical examination revealed diminished breath sound on both lungs. No lymph node swelling and hepatosplenomegaly were observed. Laboratory examinations showed a moderately elevated lactate dehydrogenase (321.1 U/L) and increased erythrocyte sedimentation rate (46mm/h). Complete blood count revealed: Hb 52g/L, platelet 12×10^9/L, leukocytes 0.9×10^9/L, with differential count of 30% neutrophils and 65.6% lymphocytes. Normal values were obtained for liver and renal functions, urine and stool routines, as well as tumor markers.

Bone marrow aspiration was performed and confirmed complete remission with total count of 4% for primitive granulocyte, promyelocyte and naïve monocytes. Then two cycles of CAG chemotherapy (aclacinomycin + cytarabine + granulocyte colony-stimulating factor) as consolidation therapy were conducted. However, 4% juvenile cells were found in peripheral blood two weeks after the second CAG regimen. Further myelocytic examination showed 15.6% leukemic cells, and leukemia relapse was confirmed.

First consultation

Dr. ZHU Hongli: The elderly patient was definitely diagnosed as acute myelomonocytic leukemia (M4b subtype). The present major problem was the therapy after relapse. In reference to previous treatments, though complete remission was not achieved after the first cycle of IA chemotherapy, an obvious decrease in primitive and naïve cells by 50% was observed and effective therapy should be considered. According to the principle of "continuous application of effective regimen", a

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second IA should be given after initial chemotherapy, but not replaced by HA. As far as his general condition was considered, despite of 65-year-old, good condition and normal functions of liver, kidney and heart were present. Several regimens were alternative. For example, addition of podophyllum (eg. etoposide) to MA (mitoxantone+cytarabine) was feasible.

Dr. DA Wanming: I agreed with hematologist A on analysis of patient's condition. The diagnosis of recurrent acute myelomonocytic leukemia (M4b subtype) was established. The chemotherapy he received included IA, HA, AMA, and CAG. The toxic effect of chemotherapy on heart and other important organs should be considered. Because of the old age, in regard to the dose and course of chemotherapy, toxic effect on organs such as heart should be considered. If MA plus etoposide could not result in remission, the chance that the patient gained another complete remission was minimal. Under such condition, the treatment strategy should be changed. The cancer-bearing survival and improvement of life quality were the main objectives. The response to MA plus etoposide should be observed. If remission could be achieved, MA plus etoposide would be continued. But if no remission, low-dose sequential chemotherapy (eg. cytarabine + amsacrine + methofrexate) was an alternative.

Dr. WANG Yuezeng: I agreed with the opinions of above two specialists. Though the functions of important organs of the patient were good, but he was already 65 years old. So monitoring of heart, liver, and kidney functions was necessary during treatment and changes of patient condition shoud be observed closely and managed in time. In addition, prophylaxis of infection is very important.

The treatment course after the first consultation

The next chemotherapy included a series of regimens as follows: the combination of arsenous acid, mitoxantrone and cytarabine, the sequential administration of cytarabine, amsacrine and methotrexate, the combination of mitoxantrone, cytarabine, and teniposide, as well as two cycles of standard IA regimen. But no remission was obtained. The ratio of leukemic cells in peripheral blood fluctuated between 77% and 97%. The general condition of the patient gradually deteriorated. The temperature fluctuated between 37.5-39.1℃. Reexamination of bone marrow revealed 65.6% of primitive and naïve monocytes. The chromosone analysis (50 metaphase) demonstrated a complicated abnormal karyotype, including del (3p11-p25), -5, +8 and add(17p11) abnormal clones, and some karyotypes had additional abnormalities, such as del(6q), del(7q22), -22, +mar1, +mar2, acex2, and DM.

The present case belonged to the subgroup of geriatric refractory and recurrent acute myelocytic leukemia with insensitivity to chemotherapy. Unfortunately, hematopoietic stem cell transplantation could not be performed because of his advanced age. For the sake of further possible treatment, the second consultation was organized.

The second consultation

Dr. LOU Fangding: The present case was an old male, and the definite diagnosis was acute myelomonocytic leukemia (M4b subtype). After second chemotherary only temporal remission was achieved, and recurrence appeared rapidly. Although a series of chemotherapy, including standard IA regimen, other first-line and second-line regimens were carried out, 60% leukemic cells in bone marrow and peripheral blood was present all the time. The clinical evidence indicated that the patient suffered from refractory and recurrent leukemia with insensitivity to many chemotherapy regimens. In consideration of his age and constitutional factor, hematopoietic stem cell transplantation was not suitable. Under such circumstance, supportive and palliative treatments should be the main measures, such as improving anemia, prophylaxis of hemorrhage, active therapy of infection, and protective isolation, in order to make

preparation for further treatment.

Dr. YAO Shanqian: I agreed with the opinion of specialist D. However, besides above supportive symptomatic treatments, chemotherapy did not seem to work and is not suitable for this patient. On the contrary, chemical drugs would add toxic side effects on important organs. Thus, cellular immunotherapy as an alternative may be considered.

Dr. HAN Weidong: I agreed with the opinions of above two specialists. Chemotherapy was not suitable to the patient. Immunotherapy can be considered. The patient was in the progression stage of leukemia, cellular immnunotherapy was used for preventing relapse under the situation of low leukemic load, but this patient was obviously different. Therefore, *ex vivo* amplification of autologous immunocytes was not applicable. The cytokine-induced killers (CIKs) are not restricted by MHC and cause little graft versus host disease (GVHD) to allogeneic recipients. It was evidenced that CIKs is a safe and effective therapy. The patient was an elderly leukemia patient, haploid HLA-matched CIKs are good option as allogeneic immunotherapy, possibly resulting in a good effect. Of course, prognosis of the case was poor despite of efficacy of CIKs because he was in prostration condition due to advanced leukemia and more than ten cycles of chemotherapy. It could be expected that CIKs may produce some effect, but poor prognosis can not be changed. At present we should consider safety in addition to therapeutic efficacy, and informed consent from his relatives is also necessary.

Dr. JI Shuquan: With regards to allogeneic CIKs for treatment of leukemia, I had some experience. Same as the opinion of specialist A, CIKs might be used after leukemic load was decreased to relatively low level. It was evidenced from clinical cases that allogeneic CIKs was safe for treating leukemia. I agreed that allogeneic CIKs could be used as first option of next therapy. In spite of scarcity of GVHD from allogeneic CIKs, attention should still be paid.

The treatment course following the second consultation

After the second consultation, chemotherapy with homoharringtonine, fludarabine phosphate, and mercaptopurine was given. White blood cell decreased to the lowest of 3.0×10^9/L, with high ratio of leukemic cells (98%). Subsequently, allogeneic CIKs from the patient's son was transfused for 4 times (effector cell count: 10^5-10^7 per each time). One week later, leukemic cell ratio in peripheral blood descended to 50%. Finally he died of respiratory failure three weeks after CIKs treatment. Autopsy under informed consent of his relatives was performed on the second day after death.

Discussion on cause of death

Dr. ZHU Hongli: The present case was an elderly male, and the diagnosis of acute non-lymphocytic leukemia was made with clinical course of more than one year. Though he received more than ten cycles of chemotherapy with fisrt-line and second line regimens of different dosages, leukemia progressed all the time. In spite of temporal remission during progression, immunotyping by cytometry confirmed only partial remission. This case was typical refractory and recurrent leukemia. Under the circumstance of no suitable chemotherapy, haploid HLA-matched CIKs immunotherapy was carried out. Leukemic cell ratio in peripheral blood decreased from 90% to 50% following treatment with CIKs, indicating effective therapy. But unfortunately he died from leukemic progression. At the same time of decrease in leukemic cells after CIKs treatment, transient skin rash of whole body (Fig 1) and mild abnormal liver function (Fig 2) occurred, suggesting that there was mild graft versus host reaction. In conclusion, haploid HLA-matched CIKs immunotherapy was safe for treatment of leukemia.

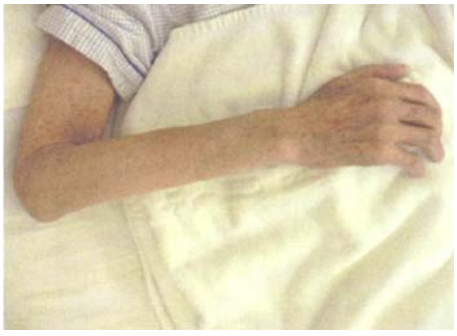
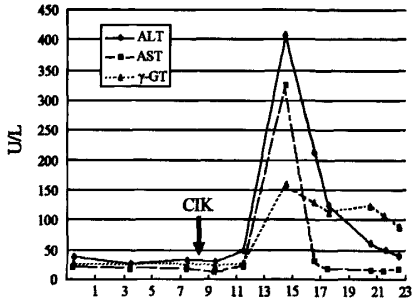


Fig 1 Skin rash of upper limb one week after infusion of haploid HLA-matched CIKs



Date from Sept 1-23, 2008

Fig 2 Changes of liver function before and after infusion of haploid HLA-matched CIKs

Dr. SONG Zhigang: The autopsy revealed acute non-lymphocyte leukemia involving multiple organs including liver, spleen, lung, kidney, alimentary tract, adrenal gland, prostate, testis, diaphragm, and mediastinal and hilar lymph nodes. In addition, hemorrhage in peripheral area of thoracic medullary canal and leukemic cells in lumen of peripheral blood vessel were observed. Histopathological examination of lung showed congestion of both lungs with hemorrhage of alveolar space and local hemorrhage and edema of inferior lobe of left lung. Hematopoiesis of ribs was extremely active, indicating that graft versus host reaction was mild. The direct cause of death was multiple organ failure and mainly respiratory failure resulting from acute leukemia involving multiple organs.

(Translator: YANG Bo)

单倍体相合CIK细胞治疗复发、难治性老年急性粒单核细胞白血病1例

1 病历摘要

患者男性，65岁，主因"间断牙龈肿痛、出血伴鼻衄3个月"于2007年10月23日入院。患者于2007年7月间断牙龈肿痛、出血，未系统治疗，后出现鼻衄。当地医院检查示：白细胞(WBC) 28.1×10^9/L，血红蛋白(Hb)75g/L，血小板21×10^9/L，原始单核细胞＋幼稚单核细胞占49%，诊断为"急性非淋巴细胞白血病M4b"。先后以IA方案(去甲氧柔红霉素＋阿糖胞苷)和HA(高三尖杉酯碱＋阿糖胞苷)标准方案化疗两个疗程，未缓解。第三疗程采用AMA方案(亚砷酸＋米托蒽醌＋阿糖胞苷)化疗，于2007年10月12日化疗结束。患者既往体健，否认高血压、糖尿病、冠心病病史；否认肝炎、结核等传染病病史。无疫区、疫水接触史。吸烟40余年，20余支/d，已戒2个月，无酗酒史。

入院情况：体温36.6℃，脉搏68次/min，呼吸18次/min，血压125/75mmHg。全身皮肤黏膜无黄染、出血点、浅表淋巴结、肝脾未触及。胸肋骨无压痛。双肺呼吸音减弱、未闻及干湿啰音。心前区无隆起，未扪及震颤，心率68次/min。辅助检查：WBC 0.9×10^9/L，中性粒细胞30%，淋巴细胞65.6%，Hb 52g/L，血小板12×10^9/L。乳酸脱氢酶321.1 U/L。血沉46mm/h。其余肝肾功能、尿便常规正常，肿瘤标志物正常。

入院诊治经过：入院后复查骨髓示原始＋早幼粒细胞＋幼稚单核细胞占4%，为完全缓解。之后予CAG方案(阿克拉霉素＋阿糖胞苷＋粒细胞集落刺激因子)巩固治疗两个疗程。第二次CAG方案化疗后2周外周血出现幼稚细胞占4%，复查骨髓幼稚细胞占15.6%。白血病复发。

2 临床病理讨论

2.1 **第一次院内会诊** 朱宏丽医师：患者为老年男

性，起病急骤。诊断为急性非淋巴细胞白血病M4b，病史清楚，诊断明确。现在主要的问题是白血病复发的治疗问题。复习病史，患者在第一个疗程的IA方案治疗后，虽然未达完全缓解，但是骨髓和外周血的原始+幼稚细胞的比例下降了一半，应该为有效。按照有效就继续应用的原则，在院外第一个IA方案之后应该继续给予一个疗程的IA方案化疗，而不应该更换HA方案。就目前来看，患者虽然65岁，但身体一般情况较好，肝肾及心脏功能正常。仍有许多方案可供选择，可在MA方案（米托蒽醌+阿糖胞苷）基础上加用鬼臼类的药物，如依托泊苷。

达万明医师：首先我同意专家A对病情进行的分析，患者目前诊断明确，为复发的急性非淋巴细胞白血病M4b，且已经进行了包括IA、HA、AMA以及CAG方案的治疗。患者为老年，65岁，在用药的剂量和疗程方面应该考虑到心脏等脏器的毒副作用，如果MA+VP16仍不能缓解，那么该患者再次达到完全缓解甚至部分缓解的可能性就非常小了。在这种情况下，就要改变策略，争取带瘤生存，以提高生活质量为主，不能一味追求缓解，实际上也做不到缓解。下一步视患者对MA+VP16方案的反应，如果达到缓解则继续应用，否则可采用小剂量序贯化疗，如阿糖胞苷+安吖啶+甲氨蝶呤等。

汪月增医师：我完全同意上述两位专家的意见。虽然该患者目前心脏、肝肾功能较好，但是毕竟已经65岁，所以在治疗过程中一定要注意监测心脏、肝肾功能变化，并密切观察病情变化，及时处理。提示，预防感染非常重要。

2.2 *第一次会诊后的治疗* 此后先后给以亚砷酸+米托蒽醌+阿糖胞苷、阿糖胞苷+安吖啶+甲氨蝶呤、米托蒽醌+阿糖胞苷+替尼泊苷、以及两个疗程的标准IA方案（去甲氧柔红霉素+阿糖胞苷）化疗。但白血病始终未缓解，外周血原幼细胞比例始终在77%～97%。患者一般情况差，体温波动于37.5～39.1℃。复查骨髓结果：原幼单核细胞比例为65.6%，染色体（50个中期分裂相）可见del(3p11-p25)、-5、+8、add(17p11)异常克隆，其中部分核型还伴有del(6q)、del(7q22)、-22、+mar1、+mar2、acex2、DM等附加异常。

患者为老年难治、复发性急性髓细胞白血病，对化疗极其不敏感，而造血干细胞移植因年龄过大而无法进行。在此情况下进行了第二次院内外会诊。

2.3 *第二次会诊记录* 楼方定医师：患者为老年男性，急性粒单核细胞白血病，诊断明确。在第2次化疗后出现短暂的缓解，但很快复发，此后进行了包括标准IA方案在内的标准一线和二线方案化疗，但血液和骨髓中的原始细胞比例始终在60%以上，这充分说明，该患者为难治复发的白血病，对多种化疗不敏感。而考虑到年龄和体质性因素，又不具备造血干细胞移植的指征。在此情况下，应该以支持和辅助治疗为主，纠正贫血、预防出血并积极治疗感染，提示做好保护性隔离，为进一步的治疗做准备。

姚善谦医师：我完全同意专家D的意见。但是，除了上述的支持对症治疗之外，化疗看来难以奏效，对该患者已不适用，反而可能会增加对机体的毒副作用。在此情况下，是否可以考虑进行细胞免疫治疗？

韩为东医师：我同意上述两位专家的意见，即化疗对该患者已经不再适用。细胞免疫治疗可以考虑。但是，该患者处于白血病进展期，一般情况下，细胞免疫治疗都是在白血病细胞负荷很低的情况下，为了预防复发而采用。而该患者显然与此不同。所以采用自体免疫细胞体外扩增并不合适。但是在免疫细胞体外扩增治疗中，有一种细胞因子诱导杀伤细胞（cytokine induced killer，CIK），由于其不受主要组织性相容性复合体（major histocompatibility complex，MHC）限制，因此对异基因的受者基本没有移植物抗宿主效应，比较安全。该患者为老年白血病患者，如果选用异基因，当然半相合更好，可能会起到事半功倍的效果。当然，即便有效，其预后也不会好。因为患者经过十余次的化疗，整个机体处于衰竭状态，而且目前为白血病终末期。单纯依靠CIK细胞免疫治疗，可能会起一定的作用，但对预后很难改变。目前我们主要考虑的除了疗效以外，还有安全性，并且需要家属知情同意。

纪树荃医师：关于异基因治疗白血病的问题，我有过这方面的经验。与A专家的意见一样，即需要把白血病的肿瘤负荷降到一个相对理想的水平，然后才可以进行。从已有的临床病例看，异基因CIK治疗白血病还是比较安全的。我同意选用异基因CIK细胞作为下一步治疗的首选。尽管罕见，但也要注意可能出现的移植物抗宿主效应的出现。

2.4 *第二次会诊后的治疗* 第二次会诊后，给予高三尖杉酯碱、磷酸氟达拉

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滨、6-巯嘌呤等药物，外周血白细胞最低下降至3.0×10⁹/L，原幼细胞比例为98%。后开始予异基因CIK细胞免疫治疗，1周后外周血白血病细胞比例下降至50%。但在CIK细胞治疗3周后，患者因呼吸衰竭而死亡，并于死亡第2天进行了尸体解剖。

3 死亡讨论

朱宏丽医师：患者为老年急性非淋巴细胞白血病，从诊断到死亡病史1年余。期间接受了多个疗程不同剂量的一线和二线治疗，但白血病始终呈进展状态。期间虽然短暂缓解，但从免疫分型上看属不完全缓解。该病例为典型的难治、复发性白血病。在化疗难以进行的情况下，开展了半相合的异基因CIK细胞治疗。在CIK细胞治疗后外周血白血病细胞比例由90%降至50%，提示治疗有效，但终因病情进展而死亡。在白血病细胞比例下降同时，出现一过性全身皮疹(图1)和肝功能异常(图2)，提示有轻度的移植物抗宿主效应，但均轻微，表明半相合CIK细胞治疗是安全的。

宋志刚医师：急性非淋巴细胞白血病伴全身多脏器累及，包括：肝、脾、肺、肾、消化道、肾上腺、前列腺、睾丸、膈肌及纵隔以及肺门淋巴结；胸段脊髓中央管周围出血，周边血管腔内见白血病细胞；双肺瘀血伴肺泡腔内出血，左肺下叶局部出血、水肿。肋骨内的造血增生极其活跃，说明移植物抗宿主效应很轻，其死亡原因为急性白血病累及全身多脏器致呼吸功能衰竭为主的多脏器功能衰竭死亡。

(参加讨论医师：杨波、卢学春、达万明、汪月增、楼方定、姚善谦、韩为东、纪树荃、宋志刚)

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单倍体相合CIK细胞治疗复发、难治性老年急性粒单核细胞白血病1例

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