

# Effective treatment of aplastic anemia secondary to chemoradiotherapy using cyclosporine A

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Aplastic anemia (AA) is a bone marrow failure syndrome that can be classified as either congenital or acquired AA. Most cases of acquired AA are idiopathic, in which the abnormal immune system attacks bone marrow hematopoietic stem cells and their microenvironment.<sup>[1]</sup> Some AA is secondary to radiotherapy and/or chemotherapy. However, most of the cytopenia can recover within 1 to 2 months after stopping the chemoradiotherapy, because bone marrow suppression therapies are devised to be reversible. Even though, some patients fail to recover from the hematopoiesis after more than 3 therapy-free months. These patients, who were diagnosed as AA after careful workup, were unable to continue with their planned chemoradiotherapy, and sometimes suffered from or died of infections or bleeding caused by severe cytopenia, or relapse from the primary tumors. The extensive use of bone marrow suppression therapy in patients with malignant tumors has been associated with an increase in therapy-related AA. Unfortunately, there are currently no guidelines or consensus on the management of these patients. In this study, we explored the efficacy and safety of cyclosporine A (CsA) in these patients.

All patients included in this study met the following criteria:

- (1) clear diagnosis of malignant tumor with no history of hematologic abnormalities before tumor therapy;
- (2) at least one lineage decreased after chemoradiotherapy and did not recover after ceasing chemoradiotherapy for at least 3 months;
- (3) diagnosed as AA according to bone marrow smear and biopsy, chromosome examinations, gene profiles for myeloid malignancies, and other related differential diagnosis workup;
- (4) had at least one of the following: hemoglobin (HGB)  $<90$  g/L, absolute neutrophil count (ANC)  $<0.5 \times 10^9$ /L, platelets (PLT)  $<20 \times 10^9$ /L; and

- (5) had a stable malignant tumor with expected survival  $>6$  months. All patients had been treated with CsA  $3-5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  for at least 6 months, with a target concentration of 100 to 200 ng/mL.

Blood transfusion was allowed, but patients did not receive hematopoietic growth factors, including eltrombopag, during the study period. Efficacy was evaluated according to international guidelines.<sup>[2]</sup> Patients were followed up for at least 1 year.

Twenty-five patients were enrolled for final analysis. Their baseline clinical characteristics before CsA are shown in Table 1. There were 8 males and 17 females, with a median age of 58 (25–76) years. There were five cases of cervical cancer, four ovarian cancers, four colorectal cancers, four urinary tumors, three breast cancers, two lung cancers, one thymic carcinoma, one tongue cancer, and one nasopharyngeal carcinoma. The median cycles of chemotherapy were three (1–8 cycles) and the median radiotherapy dosage was 45 (25–60) Gy. All patients had been treated with granulocyte-colony stimulating factor, erythropoietin, thrombopoietin, interleukin-11, or eltrombopag for at least 4 to 12 weeks with no response. The diagnosis of AA was made at a median of 4 (3–5) months after finishing the last chemoradiotherapy. Seven patients had single lineage, four had bi-lineage, and 14 had tri-lineage cytopenia. The baseline level of HGB was  $95 \pm 27$  g/L, the average ANC was  $2.0 \pm 1.9 \times 10^9$ /L, and PLT count was  $18 \pm 17 \times 10^9$ /L. For the 25 patients, the median duration of CsA treatment was 12 months (6–24 months) and the median follow-up time was 14 months (8–40 months). The CsA concentration was maintained at 100–200 ng/mL during the treatment period. After 3 months, the complete response (CR) rate was 16% (4/25), the partial response (PR) rate was 36% (9/25), and the overall response rate (ORR) was 52% (13/25). The CR, PR, and overall response (OR) rates were 24% (6/25), 40% (10/25), and

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**Table 1: Basic clinical characteristics before CsA of 25 patients with malignant tumors diagnosed as aplastic anemia after chemoradiotherapy.**

Sex	Age	Tumor type	Chemotherapy cycle	Radiotherapy dosage (Gy)	Chemotherapy regimen	Baseline blood cell count				Treatment before CsA
						WBC ( $\times 10^9/L$ )	NEUT ( $\times 10^9/L$ )	HGB (g/L)	PLT ( $\times 10^9/L$ )	
F	61	Colorectal cancer	4	0	XELOX	8.81	5.26	130	17	TPO
M	67	Colorectal cancer	5	0	FOLFOX	5.51	3.04	155	11	TPO
F	49	Breast cancer	4	0	EC + xeloda	2.25	0.53	53	18	TPO, G-CSF
M	67	Colorectal cancer	5	0	FOLFOX	2.50	0.80	81	5	TPO, cortisol, G-SCF
M	64	Urinary tumor	7	0	GP	2.00	1.35	85	5	TPO, Eltrombopag
F	45	Cervical cancer	2	0	TP	2.71	0.75	59	2	EPO, G-CSF, TPO
M	76	Urinary tumor	0	50	-	10.90	8.53	105	3	TPO
F	41	Cervical cancer	2	25	TP	2.87	1.66	89	24	TPO, cortisol
F	48	Ovarian cancer	0	40	-	2.44	0.49	85	62	TPO, G-CSF
F	56	Ovarian cancer	3	0	TC	4.76	2.98	123	14	TPO
M	64	Lung cancer	2	45	PC	3.61	1.58	77	8	Cortisol, IVIG, TPO
F	58	Cervical cancer	3	50	TP	7.49	5.48	144	7	TPO
F	45	Urinary tumor	4	0	GP	3.09	1.34	61	12	TPO, EPO, G-CSF
F	46	Ovarian cancer	3	0	TC	6.60	2.21	118	20	TPO
F	60	Cervical cancer	3	45	TP	2.67	1.69	88	8	TPO, EPO, G-CSF
M	52	Colorectal cancer	3	0	XELOX	2.50	1.27	79	24	TPO
M	46	Nasopharyngeal cancer	0	60	-	2.41	0.89	135	11	TPO
F	33	Thymic carcinoma	4	0	TC	5.46	3.20	83	61	-
F	25	Tongue cancer	3	0	DDP + 5-Fu	2.45	0.45	115	14	TPO, G-CSF
F	64	Ovarian cancer	7	0	TC	1.40	0.75	81	4	TPO
F	55	Breast cancer	8	50	AC-T	3.50	2.15	115	17	TPO, Eltrombopag
F	59	Breast cancer	6	40	TAC	2.55	1.51	73	17	Eltrombopag, TPO, cortisol
M	64	Urinary tumor	1	0	TP	2.80	1.23	87	14	IL-11
F	64	Lung cancer	2	0	PC	1.95	0.37	75	5	G-CSF, TPO
F	58	Cervical cancer	2	50	TP	2.12	1.45	84	30	TPO, Eltrombopag, IL-11

5-Fu: 5-fluorouracil; AC-T: Doxorubicin + Cyclophosphamide + Taxol; CsA: Cyclosporine A; DDP: Cisplatin; EC: Epirubicin + Cyclophosphamide; EPO: erythropoietin; F: Female; FOLFOX: Leucovorin Calcium + Fluorouracil + Oxaliplatin; G-CSF: Granulocyte-colony stimulating factor; GP: Gemcitabine + Cisplatin; HGB: Hemoglobin; IL-11: Interleukin-11; IVIG: Intravenous immunoglobulin; M: Male; NEUT: Neutrophil; PC: Pemetrexed + Cisplatin; PLT: Platelets; TAC: Taxotere + Doxorubicin + Cyclophosphamide; TC: Taxol + Carboplatin; TP: Taxol + Cisplatin; TPO: Thrombopoietin; WBC: White blood cell; XELOX: Capecitabine + Oxaliplatin.

64% (16/25) at 6 months; and 36% (9/25), 44% (11/25), and 80% (20/25), respectively, at the end of the follow-up. At the end of the follow-up, the average HGB had increased to  $100 \pm 20$  g/L, ANC to  $2.3 \pm 1.0 \times 10^9/L$ , and PLT count to  $92 \pm 81 \times 10^9/L$ . Only 15 patients tested the ratio of CD4/CD8<sup>+</sup> before and after CsA treatment and showed the value of  $1.05 \pm 1.20$  and  $1.62 \pm 2.05$ , respectively ( $P=0.263$ ). Side effects during the CsA treatment included creatinine increase ( $n=1$ , 4%), mild gingival hyperplasia ( $n=4$ , 16%), mild bilirubin increase ( $n=3$ , 12%), and gastrointestinal discomfort ( $n=3$ , 12%). All patients had stable tumor status during the follow-up period. One patient with breast cancer, who achieved CR after 1 year of CsA treatment, had four additional courses of chemotherapy and recovered well from each transient marrow suppression period. Another patient with kidney cancer, who achieved CR after 8 months of CsA, had two cytotoxic consolidation chemotherapies and tolerated well. CsA had been stopped during the chemotherapy period for these two patients.

In this study, patients with normal blood cell count before chemotherapy and radiotherapy were selected for analysis to avoid interference from the underlying blood diseases. Furthermore, all AA workups were performed at least 3 months after the stop of chemoradiotherapy to exclude transient myelosuppression. The differential tests for other diseases that may cause cytopenia were mandatory. Since these patients cannot recover from the regular dose of cytoreductive therapy, there might have other mechanisms that can cause sustained marrow failure. For instance, drugs, infections, or other unknown factors may trigger the autoimmune attack during the chemoradiotherapy and the attack lasted continuously afterward, as observed similarly in patients with primary AA.<sup>[1]</sup> Due to the small number of patients, it was hard to determine the possible risk factors like age, type of original tumors, dosage, or cycles of chemoradiotherapy for the occurring of the secondary AA, although there were more females (M/F: 8/17) in our cohort. No difference in OR rate in patients with different baseline characters was observed (data not shown), either.

There are currently no studies focusing on this type of AA. Almost all the clinical trials for AA have excluded patients with tumors; therefore, there are no guidelines or consensus for these patients. CsA is an immunosuppressive agent commonly used to treat primary AA. It may increase Treg cells and decrease immune surveillance as a result.<sup>[3]</sup> Long-term use of CsA has been reported to increase the incidence of lymphoproliferative diseases and malignant tumors,<sup>[4]</sup> and it is rarely used in cancer patients without chemotherapy. However, for those suffering from secondary AA who failed to respond to the supportive treatment with blood transfusion, hematopoietic-stimulating factors, and thrombopoietin (TPO)-receptor agonist like eltrombopag, the persistent cytopenia can cause severe complications and impair the patients' quality of life, and patients had to quit the following chemoradiotherapy, which may lead to shorter overall survival. Since patients in our study had relatively stable tumor status, they were treated with CsA after obtaining informed consent. Most patients responded to CsA, with nearly half of them responded at 3 months, 2/3 at 6 months, and 80% at a median of 14 months follow-up. The response rate seemed higher than that of primary AA, which could be explained by the relatively shorter duration and less severity of AA in our cohorts. On the other hand, the adverse events were similar to those with primary AA,<sup>[5]</sup> including elevated creatinine and bilirubin, gingival hyperplasia, and gastrointestinal discomfort. However, most of the symptoms were mild and were improved by dose adjustment.

Due to the concerns about the tumor progression, patients in our study were closely monitored the tumor status during the follow-up period. In a median of 14-month follow-up, no progression of the primary tumor was noticed. Meanwhile, two patients completed their following chemotherapy after hematological remission from CsA treatment. Since all the patients had malignant tumors, they may relapse anyway even without CsA. If they were not treated with CsA, they may not have the chance for further anti-tumor therapy due to cytopenia and would relapse in a shorter time. Even though clear communication with patients before CsA and close monitoring of tumor status is needed, meanwhile, a longer time of follow-up with more patients in a well-organized study should be considered in the future.

In conclusion, we demonstrated that CsA was effective in cancer patients suffering from chemoradiotherapy-related

AA, with mild side effects. Although the number of patients was less and the follow-up time was relatively short, these results will provide a reference for future treatment selection of these patients.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) or his/her guardian has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients or his/her guardian understand that his/her/their name(s) and initials will not be published and due efforts will be made to conceal his/her/their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

None.

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