Treatment of ANCA-Positive, Pauci-Immune Extracapillary Glomerulonephritis with Etoposide

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Dear Sir,

Traditional treatment of severe connective tissue disease, especially Wegener's granulomatosis (WG), consists of corticosteroids combined with azathioprine or cyclophosphamide. A few patients are resistant to this therapy, and in a recent report, which included patients suffering from antineutrophil cytoplasmic autoantibody (ANCA) associated diseases, the patient survival at the 75th per-centile was only about 15-16 months [1]. D'Cruz et al. [2] reported on the response of cyclophosphamide-resistant WG to etoposide. We report on a patient suffering from severe pauci-immune, ANCA-positive extracapillary glomerulonephritis who did not tolerate conventional treatment, but who obtained a complete remission after treatment with etoposide. Treatment with etoposide was associated with significantly less bone marrow suppression as compared with azathioprine.

The patient, a 47-year-old man, developed malaise and arthralgia in November 1991. In December 1991 he was admitted to the hospital where arthritis affecting both hips, knees, ankles, shoulders, and elbows was noted. Apart from arthritis, the patient suffered from

ANCA

Az

Hb

Epo

Fig. 1. a Increasing ANCA levels (normal range < 3) despite increasing doses of azathioprine ($\times$ IO = daily intake, mg). b B-Hemoglobin normalized (normal range 8.6-10.8 mmol/l) in

spite of tapering erythropoietin from 12,000 to 3,000 U/week. The arrow in a and b indicates cessation of azathioprine and initiation of etoposide therapy. Az = Azathioprine; Hb = B-hemoglobin; Epo = erythropoietin ($\times 1,000 = \text{U/week}$).

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paresthesia in the lower limbs and later on from abdominal pain. Several blood tests and chest X-ray, muscle biopsy, and abdominal aortography, including right renal artery and truncus celiacus, were normal. During the following 2 months the patient's renal function deteriorated, the serum creatinine level increased rapidly from 81 to 327 $\mu\text{mol/l}$, and proteinuria developed. On February 14, 1992, the patient was transferred to the Department of Nephrology, where a course of plasma exchanges (7×4 liters) was performed, as the serum ANCA levels were found to be significantly elevated. At the same time combined immunosuppression with prednisolone (1 mg/kg/day) and azathioprine and cyclophosphamide (both 1.33 mg/kg/day) was initiated. A kidney biopsy specimen showed severe pauci-immune extracapillary glomerulonephritis (80-90% crescents). During the next 4 months ANCA disappeared, and the serum creatinine level stabilized at around 225 $\mu\text{mol/l}$. Because of severe bone marrow suppression, the patient suffered a severe herpes simplex infection. So treatment with cyclophosphamide had to be canceled on March 5, 1992. From May 12, 1992, azathioprine had to be reduced to 1 mg/kg/day because of severe anemia.

Figure 1 shows that, in spite of initiating treatment with erythropoietin (June 2, 1992) and increasing the dose initially to 100 U/kg/week and later on to 160 U/kg/week, B-hemoglobin only increased from 4.8 to maximal 7.4 mmol/l (February 1993), and serum ANCA reappeared and was still increasing from January 1993 in spite of increasing the dose of azathioprine to 1.67 mg/kg/day which resulted in a drop in B-hemoglobin to 5.2 mmol/l. Therefore, on May 18, 1993, azathioprine was stopped, and treatment with etoposide (100 mg/day for 1 week alternating with 3 weeks off treatment) was started. This change resulted in disappearance of serum ANCA within 3 months, and the B-hemoglobin levels normalized in spite of tapering erythropoietin to 40 U/kg/week. During the last 18 months the renal function has remained stable with serum creatinine levels around 225 $\mu\text{mol/l}$.

Etoposide arrests DNA replication. It is most often used in combination regimens in small-cell lung cancers, testicular teratomas, and lymphomas. In the past D'Cruz et al. [2] reported on the use of etoposide to induce remission in a patient suffering from cyclophosphamide-resistant WG. Our patient, who was suffering from ANCA-positive, pauci-immune extracapillary glomerulonephritis, represents a case in whom usual immunosuppression was insufficient to control the disease and was accompanied by unacceptable bone marrow suppression. Etoposide induced complete remission and apparently significantly less bone marrow suppression.

References

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ANCA-Positive Glomerulonephritis and Etoposide