Cytotoxic Chemotherapy and Viral Infections: the Role of Acyclovir

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The use of cytotoxic regimens in the treatment of malignant disease is associated with an increased risk of opportunistic infection. Bacterial and fungal infections are well recognised, but viral infections tend to have been ignored. With the advent of effective non-toxic antivirals (of which acyclovir is the first), the management of herpes viral infections is now possible. This article describes the incidence of viral infections in patients in the care of the medical oncology service in a year, and reviews an open trial of acyclovir used intravenously to treat 28 infections in patients who might have been excluded from controlled trials. The aim is not to confirm the efficacy of acyclovir, but to describe its routine use in ill, immunosuppressed patients.

Patients and Methods

Before 1981 few patients in the medical oncology ward had routine virological investigations during periods of infection. Since April 1981 viral infections have been sought in all patients with unexplained fever, sore mouth or oral ulceration. In addition, leukaemic patients receiving chemotherapy to induce remission have had surveillance virological screening. Specimens taken included swabs from the throat, skin and oral lesions, sera, and on occasion faeces, urine and cerebrospinal fluid.

During the year under review 156 patients, the majority with leukaemia, non-Hodgkin’s lymphoma, or carcinoma of breast or bronchus (Table 1) had virological investigations during periods of infection; 668 specimens were tested and 28 courses of acyclovir were given. The indication for treatment depended upon virological investigations but the decision to administer or withhold acyclovir was a clinical one. Acyclovir dosage was 5 mg/kg three times daily for herpes simplex virus (HSV) and 10 mg/kg t.d.s. for varicella zoster (VZ) by intravenous infusion over one hour. A course of treatment usually consisted of 15 doses.

| Diagnosis                                      | No. of patients |
|-----------------------------------------------|----------------|
| Acute leukaemia (lymphoid or myeloid)         | 37             |
| Carcinoma of bronchus                         | 34             |
| Non-Hodgkin’s lymphoma                        | 25             |
| Carcinoma of breast                           | 17             |
| Hodgkin’s disease                              | 10             |
| Melanoma                                       | 10             |
| Sarcoma                                        | 6              |
| Carcinoma of ovary                            | 5              |
| Other—                                        |                |
| haematological malignancy                     | 3              |
| chronic leukaemia                              | 2              |
| myeloma                                        | 2              |
| unknown primary carcinoma                      | 2              |
| yolk sac tumour                                | 1              |
| carcinoid tumour                               | 1              |
| gastric carcinoma                              | 12             |
| Total                                          | 156            |

Most patients had received chemotherapy within the previous six weeks, and 99 (63 per cent), had received daunorubicin, thioguanine and cytosis arabinoside for acute myeloid leukaemia[1]; vincristine, adriamycin and prednisolone (VAP) for lymphoma[2] or acute lymphoblastic leukaemia; or a moderate dose of cyclophosphamide for carcinoma of the bronchus[3] or breast.

Table 1. Diagnoses in 156 patients subjected to virological examination.

Laboratory Methods

Virus Isolation. Swabs were taken into virus transport medium and subsequently inoculated into MRC5 human fibroblast and BK tissue cultures; viruses were identified by neutralisation tests.

Electron Microscopy (EM). Material from lesions was placed on microscope slides and dried in air. The material was later re-suspended in distilled water and a drop placed on a formvar-carbon support film on an EM grid.

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The film was then stained with 3 per cent PTA (pH 6.5) and examined under the electron microscope (AE1, EM801 or ME6B). Photographs were taken of all positive samples.

**Serology.** Sera taken on admission, and thereafter as clinically indicated, were tested for antibodies to a range of viruses by standard complement fixation techniques. When indicated, other investigations were carried out (e.g. immunofluorescent tests for Epstein-Barr (EBV) VCA antibody, tests for Q fever, *Legionella pneumophila* and leptospira).

**Results**

Table 2 shows the results of the virological investigations. In addition, a total of 154 specimens were taken from 90 patients and investigated by serological techniques; 26 patients (29 per cent) had evidence of viral infection as shown by a fourfold rise in titres. Of 41 specimens, 20 (49 per cent) were shown by electron microscopy to be positive for herpes virus.

**Table 2. Viral isolates from patients with malignancy.**

| Site of viral isolate | No. of patients tested | No. with positive viral culture |
|-----------------------|------------------------|--------------------------------|
| Skin                  | 34                     | 15 (VZ 5, HSV 10)              |
| Mouth                 | 34                     | 13 (All HSV)                  |
| Throat                | 109                    | 27 (HSV 25, p’flu 2)           |
| Nose                  | 22                     | 4 (All HSV)                   |
| Faeces                | 10                     | 1 (ECHO 19)                   |
| Urine                 | 10                     | 0                             |
| CSF                   | 6                      | 0                             |
| Eye                   | 6                      | 0                             |
| Postmortem samples    | 3                      | 0                             |

VZ = varicella zoster; HSV = Herpes simplex virus; p’flu = parainfluenza virus.

**Proven Viral Infections**

Of the 156 immunosuppressed cancer patients (35 per cent) had proven viral infections (Table 3). In all, 87 viral infections were seen, some patients experiencing more than one infection. In the 37 acute leukaemic patients subjected to more rigorous cytotoxic therapy and longer periods of leucopenia, 24 (65 per cent) experienced 43 proven infections. These results exclude 13 other patients with clinical evidence of HSV or VZ infection which was unsupported by laboratory evidence, and one girl with probable rubella had only one serum sample taken (rash and rubella titre of 1/1,280).

The infections diagnosed are summarised in Table 3. It is shown that the majority of infections (69 of 87—79 per cent) were of the herpes virus group.

**Sore Mouth and Oral Ulcers**

Of 34 patients 13 (38%) (Table 2) had a possible viral cause for their infection. Of 10 leukaemic patients with oral ulcers or soreness, 8 had proven HSV infections.

**Skin Lesions**

Of 34 patients who had skin swabs taken 15 (44 per cent) had proven viral infections (Table 2). Ten were due to HSV, and five to herpes zoster. There was a high false negative rate (10 of 17) for clinical cold-sores; in retrospect this was due to faulty technique (dry swabs being applied to dry crusts). There were false negatives among swabs taken for skin rashes, e.g. four swabs done in one patient with chickenpox showed no viral growth, but EM was positive. Of nine swabs from genital lesions two grew HSV, three failed to grow virus, but treatment with acyclovir resulted in rapid healing and temperature lysis. The remaining swabs showed a bacterial or fungal cause of the genital lesions.

**Acyclovir Treatment**

Twenty-one immunosuppressed patients were treated with 28 courses of intravenous acyclovir. The underlying diagnoses were acute leukaemia (13), non-Hodgkin’s lymphoma (3), carcinoma of the bronchus (3), and Hodgkin’s disease (2). The 28 courses of treatment were given for shingles (7), cold-sores and pyrexia (6), mouth ulcers (6), chickenpox (4), and rash with pyrexia and high EBV VCA antibody levels (2), genital herpes (1), cold-sores and oral ulcers (1), and pyrexia with sore mouth (1).

In 21 instances cytotoxic chemotherapy had been given to the patient within three weeks of developing the infection treated by acyclovir. Most of the patients were leucopenic at the onset of acyclovir treatment, the median being $1.0 \times 10^9$/litre, and after it (median $1.2 \times 10^9$/litre).

**Response to Acyclovir**

Herpes simplex infections, usually cold-sores associated with pyrexia, or oral ulcers interfering with eating and
drinking, responded readily to acyclovir in 10 of 14 instances. There were two episodes of clinical resistance in two leukaemic patients with tongue ulceration. In both cases prolonged courses of acyclovir were given (15 days and 11 days) at increased dosage (20 mg/kg t.d.s. and 10 mg/kg t.d.s.). In both cases viral isolates were positive at the end of treatment. Viral cultures are now being analysed for resistance to acyclovir. One episode of partial viral resistance responded to increased acyclovir at 10 mg/kg t.d.s. One patient who died on the fourth day of treatment was not assessable (widespread leukaemic blasts at postmortem but no viral growth).

Eleven courses of acyclovir were given for VZ infection. One was for a possible second episode of chickenpox reactivation in a patient who eventually responded to metronidazole. With hindsight, this was not a viral infection. Of the other 10 courses, 9 were associated with symptomatic improvement, as assessed by decreased pain after 2-3 days and no new lesions after 48 hours' treatment. The time to the loss of the last crust varied from seven to 48 days, depending upon the area of ulceration at presentation. One patient who did not benefit had five days of shingles rash with 80 per cent involvement on the skin in the 5-7th thoracic dermatomes and superficial skin gangrene at presentation. Distant lesions did not develop but deep ulceration occurred, the last scab being lost at 46 days. Recent serial EM studies of lesion fluid from a patient with disseminated shingles have shown that viral particle numbers fall and structural changes occur during acyclovir treatment (Figs 1 and 2).

One course of acyclovir for clinical genital herpes with negative culture resulted in temperature lysis at three days and total healing at 13 days.

Two courses of acyclovir were given to a man with high EBV titres (1/1,280 with positive monospot), fever and rash. His temperature settled on the third day. On the second occasion of fever, after further chemotherapy for leukaemia, he did not respond to broad spectrum antibiotics or miconazole. In view of the possibility of recurrent EBV infection, further acyclovir was given, without response. He died, and Torulopsis glabrata and Aeromon-ium sp. were found at postmortem.

Of the 21 patients with fever at the onset of acyclovir treatment, 10 had lysis of the fever by the second day, 16 by the third day and 18 by the sixth day. Three pyrexias were unresponsive to acyclovir, one associated with clinically resistant HSV tongue ulcers, one with possible EBV relapse and death from fungal infection, and one with a possible reactivation of chickenpox that responded to metronidazole.

**Acyclovir in Pregnancy**

A 23-year-old woman with acute myeloid leukaemia (AML) received two courses of acyclovir during pregnancy for proven HSV infection and pyrexia while on broad spectrum antibiotics. One each occasion she was very ill and had a rapid lysis of fever at 18 hours and 24 hours. The pregnancy was at 17 weeks on the first occasion and 22 weeks on the second. A normal healthy daughter was born at term; she is developing normally at 9 months.

**Fig. 1.** Photograph of EM of one of many herpes viruses isolated from shingles rash before acyclovir, clearly showing the viral structure and intact cytoplasmic envelope of the herpes virus.

**Fig. 2.** Photograph of EM of one of the few herpes viruses seen after three days of acyclovir. Loss of viral structure and fragmented cytoplasmic envelope are shown. (Same patient as in Fig. 1.)


**Acyclovir in Renal Failure**

A woman with septicemia developed acute renal failure (creatinine clearance 3 ml/min, serum creatinine 1.03 μmol/litre, and urinary output 2-3 litres/day). Four days later she developed severe perineal shingles and fever. She was already on broad spectrum antibiotics. Acyclovir was started at 5 mg/kg daily for five days. Her urine output remained constant and renal function gradually improved during the course of acyclovir. New lesions ceased to form after the second day, and the fever lysed on the third. Acyclovir levels 24 hours after the last dose were 8.8 μmol/litre on the first day and 2.1 μmol/litre on the fifth day.

**Early Relapse after Acyclovir**

Early relapse was observed twice. A woman with shingles of the C2/3 area received five days of acyclovir and was discharged with almost complete healing. She returned six days after the cessation of acyclovir with a one-day history of generalised rash. This was virologically confirmed as varicella zoster, and treated with acyclovir 10 mg/kg t.d.s. for five days. Most of the lesions had healed at seven days and total scab loss occurred at 14 days. No further relapse occurred.

The second patient also had chickenpox (EM positive). He responded well to acyclovir 10 mg/kg t.d.s. for 15 days, becoming apyrexial on the sixth day. Four days after stopping acyclovir the rash became more florid, with new papules but no vesicles. He again became pyrexial and responded to another course of acyclovir. Temperature lysis occurred at 48 hours, with loss of papules at three days. Because of the low platelet count skin biopsy was not possible and virological confirmation of relapse was impossible. A third course of acyclovir given when he was very ill and pyrexial shortly afterwards had no effect, and although bacteriology was negative he responded to empirical treatment with metronidazole.

**Adverse Effects of Acyclovir**

In patients receiving multiple treatments, including cytotoxic agents, it is difficult to attribute adverse effects to one therapy. We have seen two patients with reversible peripheral neuropathy possibly related to acyclovir. One patient had three courses of acyclovir for chickenpox, and developed numbness of the feet without neurological abnormality. Serum B12 and folate were normal, and his gait gradually improved over five weeks. His acyclovir levels were 2.01 μmol/litre five hours after acyclovir infusion. The other patient had 15 days of acyclovir at 10 mg/kg t.d.s., then 20 mg/kg t.d.s. for three days without effect on his HSV tongue ulceration and fever. Acyclovir was discontinued because of clinical resistance. He had intravenous feeding and vitamins until the ulcers healed (after bone marrow recovery following VAP treatment). He had also received 12 mg of vincristine over six weeks. His walking gradually improved over 10 weeks. The acyclovir levels were 11.98 μmol/litre five hours after acyclovir infusion.

**Discussion**

The results showed that viral infections are common in the immunosuppressed, especially in leukaemia (65 per cent proven infections). The infections were caused mainly by herpes viruses, which were associated with reactivation and latency. Reactivation may occur in many tissues, and fatal herpetic viraemia may occur without a skin rash[4].

A recent paper showed that 12 of 14 patients developing stomatitis during cytotoxic chemotherapy grew HSV[5]. Of our leukaemic patients with oral symptoms following chemotherapy eight of 10 grew HSV. The unthinking attribution of oral symptoms to disease or cytotoxic treatment clearly requires some revision. The serology results showed five patients with rising antibody titres to HSV; seroconversion does not often follow reactivation of HSV[6].

One patient had an ECHO 19 gastroenteritis, and the presence of enteroviral infection during marrow transplantation is associated with increased mortality[7].

It is fortunate that there is an effective antiviral agent, acyclovir, to combat the high incidence of herpes viral infection. Acyclovir inhibits HSV and VZ replication, and has been shown to be effective and non-toxic in controlled trials in immunosuppressed patients[8-10].

Twenty-eight courses of acyclovir were given to patients who might not have been eligible for clinical trials (e.g., pregnant women and those with renal failure). We have experienced no problems with phlebitis or rises in serum creatinine in that they did not occur; however, problems have been described in other papers[9, 11]. The two cases of reversible peripheral neuropathy might have been due to acyclovir. HSV responded readily, with lysis of fever and lesion healing, except in two patients with tongue ulcers, who showed clinical resistance. Resistance to acyclovir has been described elsewhere[12, 13]. Resistance to a drug now widely available may bring future treatment problems. Acyclovir prevented the dissemination of VZ, and new lesions ceased appearing by the second day of treatment. Our patient with EBV infection responded to the first course of acyclovir but later died from a fungal infection. This may have been due to further immunosuppression by the virus[14].

Herpes virus infections are common in the immunosuppressed, and especially if causing oral ulcers, may not be diagnosed correctly without virological study. Acyclovir lacks the toxicity of previous antivirals and may be of benefit prophylactically to patients in whom recurrent herpes causes serious morbidity during chemotherapy. We know intravenous acyclovir is safe and effective and are now evaluating prophylactic oral acyclovir in immunosuppressed patients.

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Not By, But After

One of the summer-time pleasures of working at the College was the opportunity it gave to wander in Regent's Park during the lunch hour and admire the many different species of fuchsia that occupied several of the beds facing the College. The fuchsia has been a favourite of mine since boyhood, when I discovered one growing in my grandmother's front garden. Named after Leonhart Fuchs, I had expected, when looking for an illustration, to find one in his herbal; it was not, however, named by him. Father Plunier was the first to describe and draw the fuchsia in his Nova plantarum Americanarum genera, 1703.

Fuchs was born at Wemding in Bavaria in 1501; he matriculated at the University of Erlurt in 1513, distinguishing himself in Greek and Latin studies. Turning his attention to the study of medicine he went to Ingoldstadt, where he came under the influence of Luther's writings and was won over to the reformed faith. He took his doctor's degree there in 1524 and shortly after began to practise in Munich. He presently returned to Ingoldstadt as professor of medicine. In 1529, an outbreak of sweating sickness spread through Germany; Fuchs provided a successful treatment and increased his reputation thereby. By now he was in great demand as both physician and lecturer, and received offers of appointments abroad, including one to become physician to the King of Denmark. All of these he refused. In 1533 he left the Catholic town of Ingoldstadt to become professor of medicine at the new Protestant University of Tübingen.

Notwithstanding the demands of his medical work, Fuchs found time to produce a botanical masterpiece, the De historia stirpium, a handsome folio volume published at Basle in 1542. For him it was a labour of love. Nothing in this life, he felt, was more pleasant or delightful than to wander through woods and over mountains and plains which were adorned with flowers and plants of various sorts, and to gaze intently upon them. The pleasure was enhanced if there was also knowledge of the virtues and powers of these plants. Fuchs was indignant that medical men had little of such knowledge. Doctors, he claimed, tended to rely on the largely illiterate apothecaries, who, in their turn, depended on old peasants who gathered roots and herbs. Fuchs was only too well aware of the possibility of error that could ensue, with the likelihood of a patient being poisoned rather than cured if plants were not properly recognised. In fact Fuchs' first contribution to botanical literature consisted of critical remarks on medicinal plants written for Brunfels' Kreuterbuch.

The materia medica of the sixteenth century was still based on classical authorities; thus the plant descriptions in Fuchs' herbal contained little that was original, being based on those of Dioscorides, Pliny, and Galen. The plants are arranged in the order of the Greek alphabet; but the chapter headings are in Greek and the accompanying plant figures are labelled in Latin and German, sometimes making it difficult to find a plant. Fuchs' use of 'masculine' and 'feminine' tends to mislead since this refers not to any sexual characteristics, of which Fuchs was unaware, but rather to the stronger or weaker qualities of a species. A full glossary of technical terms continued on page 73