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The development of BVDU: An odyssey

Erik De Clercq

Abstract

Brivudin, ((*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) can be considered the gold standard for the treatment of varicella-zoster virus (VZV) infections, such as herpes zoster (shingles). It is available for clinical use in most European countries (except for the UK) and over the whole world (except for the US and Canada). Besides VZV its activity spectrum also includes various other herpesviruses, such as herpes simplex virus type 1 (HSV-1). Its activity against VZV and HSV-1 depends on phosphorylation by the virus-encoded thymidine kinase (TK). In its active form (BVDU TP or BVDU 5'-triphosphate), it can act as both substrate and inhibitor of the viral (i.e., HSV-1) DNA polymerase. It has proven to be effective against herpes zoster, including post-herpetic neuralgia (PHN). It is contra-indicated in patients concomitantly treated by 5-fluorouracil (FU), since its degradation product, (*E*)-5-(2-bromovinyl)uracil, is inhibitory to the catabolism of FU, which may enhance the toxicity of the latter. A new compound, the bicyclic nucleoside analogue (BCNA) Cf-1743, has been described, which is a more potent inhibitor of VZV replication than BVDU and which does not interfere with the catabolism of FU. It is applicable orally, as its 5'-valine ester FV-100 (Fermavir), but has not (yet) been marketed for clinical use.

Keywords

BVDU, VZV, HSV-1, TK (thymidine kinase), PHN, herpes zoster, FU (5-fluorouracil)

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History

BVDU was originally synthesised in the laboratory of Richard T. ('Dick') Walker, led by Prof. Stanley ('Stan') Jones at the University of Birmingham in the UK, by a PhD student called Phil Barr. It was part of a project aimed at developing radiosensitizing agents.

Following the conversation between R.T. Walker and E. De Clercq at the Symposium on Synthetic Nucleosides, Nucleotides and Polynucleotides (Max-Planck-Institut für Biophysikalische Chemie in Göttingen on 3–5 May 1976) (Figure 1), R.T. Walker passed BVDU as part of several other related analogues onto E. De Clercq, for antiviral evaluation. Anita Van Lierde was the technician working with Erik De Clercq. She routinely tested antiviral activity for three viruses: vaccinia virus (VV), herpes simplex virus (HSV) and vesicular stomatitis virus (VSV). At his first visit to the lab, when R.T. Walker inquired about the antiviral results, A. Van Lierde had those obtained for VV and VSV at hand. There was no activity against VSV, only weak activity against VV and those were the data communicated to R.T. Walker, before he flew back to Birmingham. The next day she also obtained the results for HSV, and here potent activity was observed.

The anti-HSV data of BVDU were so overwhelming, that E. De Clercq decided to deliver a communication of the results, entitled 'Comparative study of the potency and selectivity of anti-herpes compounds', in Prague at a meeting organised by Peter Langen and Jan Skoda (Twelfth Meeting of the Federation of European Biochemical Societies (FEBS), Post-Congress Symposium on Antimetabolites in Biochemistry, Biology and Medicine, Prague, Czechoslovakia, 10–12 July, 1978). R.T. Walker also presented the first results of BVDU[1] shortly after E. De Clercq did. The conference in Prague took place in 1978, a few months after the antiviral activity for acyclovir had been reported in Nature[2] (a few months earlier Gertrude Elion and coworkers had announced that acyclovir was specifically recognised as a substrate for phosphorylation by the HSV-encoded TK[3]. Acyclovir was then further developed

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Figure 1. Group picture (private collection E. De Clercq) taken at Symposium on Synthetic Nucleosides, Nucleotides and Polynucleotides, Max-Planck-Institut für Biophysikalische Chemie, Göttingen, Deutschland, 3–5 May, 1976.

as an anti-HSV agent by Burrough Wellcome and would become the 'gold standard' for the treatment of HSV infections.

In 1979 (7–18 May), E. De Clercq together with R.T. Walker and Fritz Eckstein organised a NATO Advanced Study Institute (ASI) in Sogesta (close to Urbino in Italy). The meeting was also organised as a FEBS symposium, so as to allow participants from Eastern Europe (behind the iron curtain). One of these participants was Peter Langen from East Berlin (Berlin-Buch), who presented at this symposium antiviral data on the 1-bromovinyl-2'-deoxyuridine (Figure 2) that were remarkably similar to the antiviral data we had obtained for BVDU ((*E*)-5-(2-bromovinyl)-2'-deoxyuridine). This is not surprising, since the East-Germans had erroneously interpreted their (*E*)-5-(2-bromovinyl)-2'-deoxyuridine as 1-bromovinyl-2'-deoxyuridine[4].

On 4 November 1981, I presented a talk on the antiviral potential of BVDU in Berlin-Buch with Peter Langen as my host, after I had given similar presentations at Johns Hopkins University (Baltimore, 15 May 1981), Sophia Antipolis (France, 3–4 June 1981), Harvard University (Boston, 29 June 1981), Stanford University (18 August 1981), University of Alberta (Edmonton, 21 August 1981), G.D. Searle Company (Chicago, 24 August 1981), and Yale University (New Haven, 26 August 1981). On 12 May 1982, I talked on BVDU at the Searle branch of G.D. Searle in High Wycombe, UK. While the East-Germans had started the clinical development of BVDU that led to the commercialisation of BVDU by Berlin-Chemie for the treatment of herpesvirus infections, we published our first paper on the activity of BVDU against HSV-1 in 1979 in PNAS[5], followed by the first clinical results on the activity of BVDU in the treatment of VZV infections (herpes zoster) in 1980[6].

In 1979, we licenced the antiviral activity of BVDU to G.D. Searle UK (host: Dr A. J. Hale), which assured me of their interest in the clinical development of BVDU. From the gathering in Chicago on 24 August 1981 (host: Dr D. Azarnoff), I sensed that the UK interest was not shared by the US headquarters of G.D. Searle. A few months later (12 May 1982), when we (Prof. Piet De Somer and I) were summoned for a meeting in High Wycombe, we were told by Daniel Azarnoff that Searle would discontinue the further development of BVDU. To appease the ordeal, they agreed to provide us with the whole stock (raw material and gelatin capsules) of BVDU that they had prepared in the meantime.

Then started the search for a new partner for BVDU development, but all of our attempts to finalise a partnership (e.g., Beecham, Astra) failed. In the meantime, the East-Germans (Peter Langen, Hans Rosenthal) had become more successful and had brought BVDU, under the trade name of Helpin® (Berlin-Chemie), to the market in the former DDR. Berlin-Chemie would later be taken over by Menarini (Italy).

Activity spectrum and mechanism of action

From the antiviral activity spectrum of BVDU (Figure 3), it is evident that it is exquisitely active against HSV type 1

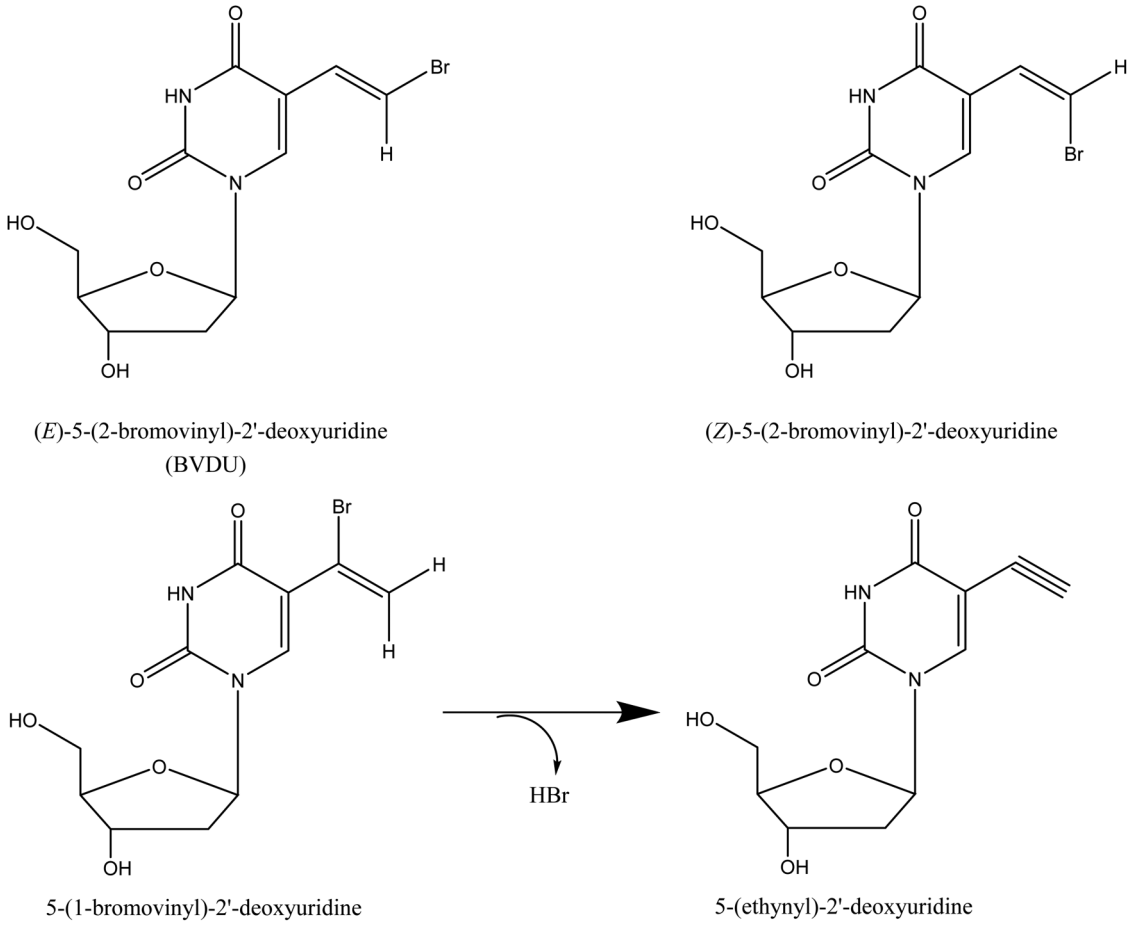

Figure 2. Structural formulae of BVDU ((*E*)-5-(2-bromovinyl)-2'-deoxyuridine) as opposed to (*Z*)-5-(2-bromovinyl)-2'-deoxyuridine and 5-(1-bromovinyl)-2'-deoxyuridine.

(HSV-1) and VZV, while minimally active against HSV type 2 (HSV-2)[7]. This is due to the fact that the thymidine kinase (TK) encoded by HSV-1 and VZV readily phosphorylate BVDU onto BVDU diphosphate (BVDU DP), whereas the HSV-2 TK phosphorylates BVDU onto the monophosphate (BVDU MP)[8], from where cellular thymidine kinases have to take over the phosphorylation process. Anyway, the active metabolite of BVDU is the 5'-triphosphate (BVDU TP), which can act as both an inhibitor and substrate of the viral DNA polymerase (Figure 4). Consequently, BVDU TP, if incorporated as substrate or acting as inhibitor of the viral DNA polymerase, serves as inhibitor of the viral DNA synthesis.

BVDU in the treatment of herpes zoster

At his visit to Leuven in 1984, Prof. Hans Rosenthal and I decided to carry out a comparative clinical study of acyclovir versus BVDU in the treatment of herpes zoster. This study would be performed under the auspices of Prof. Peter Wutzler. I bought acyclovir for this study, whereas BVDU would be delivered by the East-Germans as the compound was synthesised in East Germany. BVDU would be administered perorally (p.o.) at the dosage which we had used in our previous study[6], whereas acyclovir would be administered by the intravenous (i.v.) route, as at that time, only intravenous administration had been approved for the treatment of herpes zoster. It took a decade before the comparative clinical study of i.v. acyclovir versus p.o. BVDU was completed, but when it was[9], it clearly showed that at the indicated dosages and routes of administration, both acyclovir and BVDU were clearly effective in suppressing herpes zoster, as particularly evident from the shortened time for new lesion formation (Figure 5).

BVDU proved superior to acyclovir in reducing the time to blistering (from 18 h (acyclovir) to 13.5 h (BVDU)) (Figure 6)[10]. When the treatment (BVDU 125 mg once daily for 7 days, or acyclovir 800 mg 5 times daily for 7 days) was terminated, monthly prevalence of postherpetic neuralgia (PHN) for several months thereafter also showed a clearly faster response with BVDU than with acyclovir (Figure 7)[11]. As compared to famciclovir (Famvir®) in the treatment of herpes zoster, median duration of PHN, BVDU clearly achieved a shortened duration, both in the overall population and subgroup of elderly patients (Figure 8)[12].

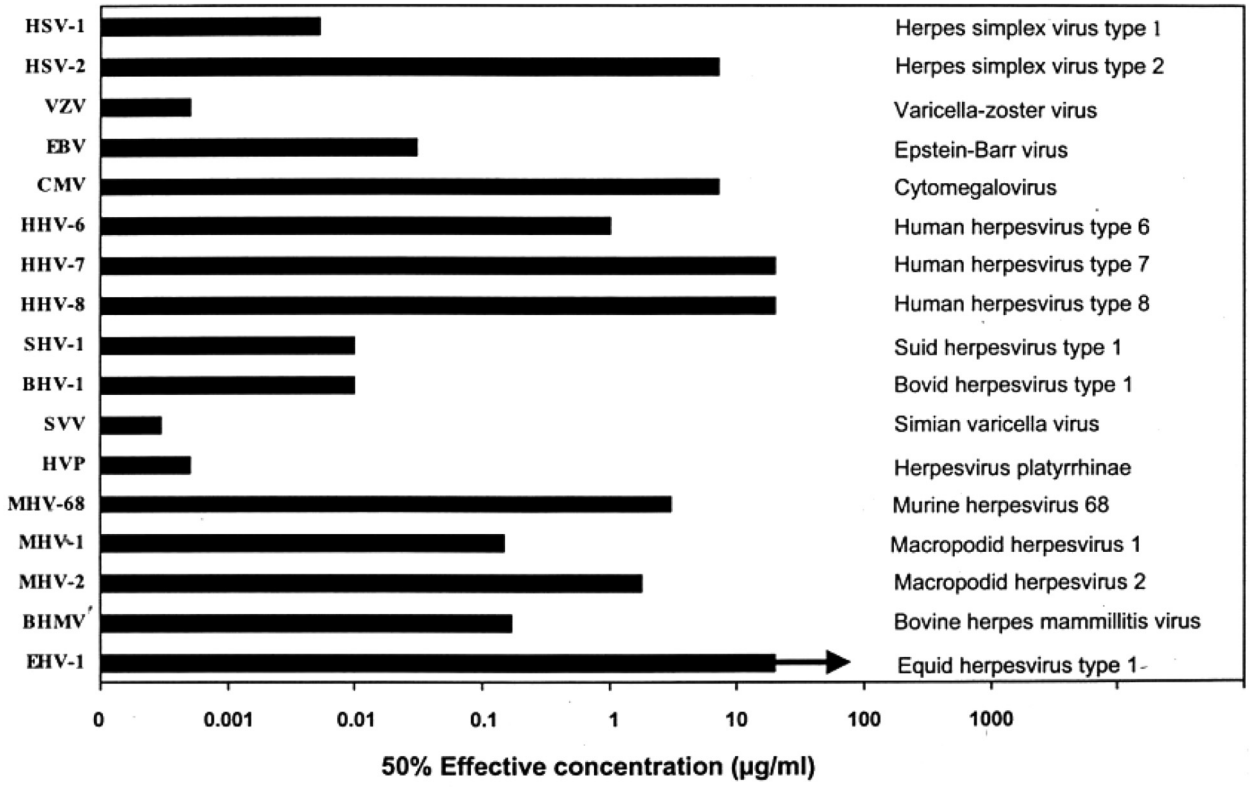

Figure 3. Antiviral activity spectrum of BVDU[8].

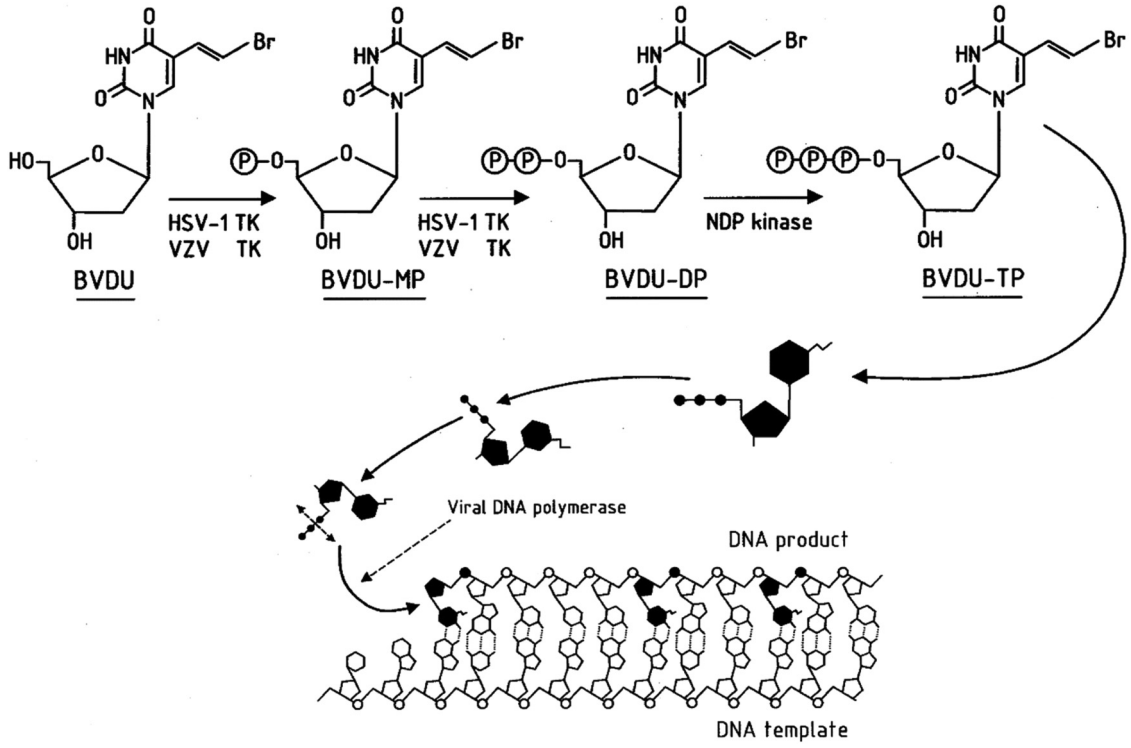

Figure 4. Mechanism of action of BVDU[8].

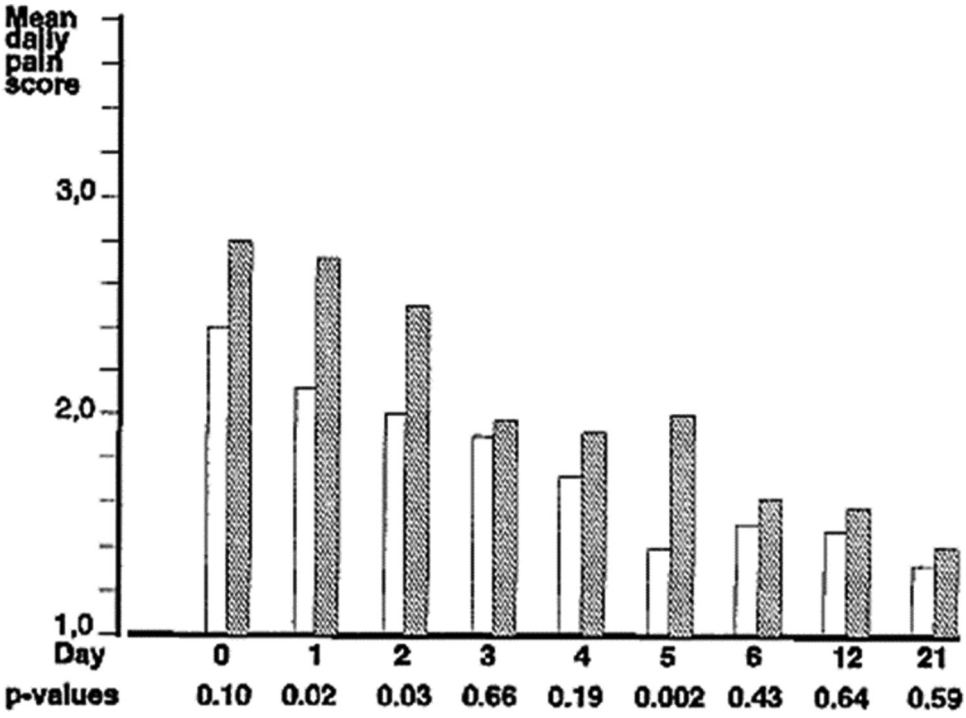

Figure 5. Mean pain scores in patients treated with brivudine (□) or acyclovir (▨)[9].

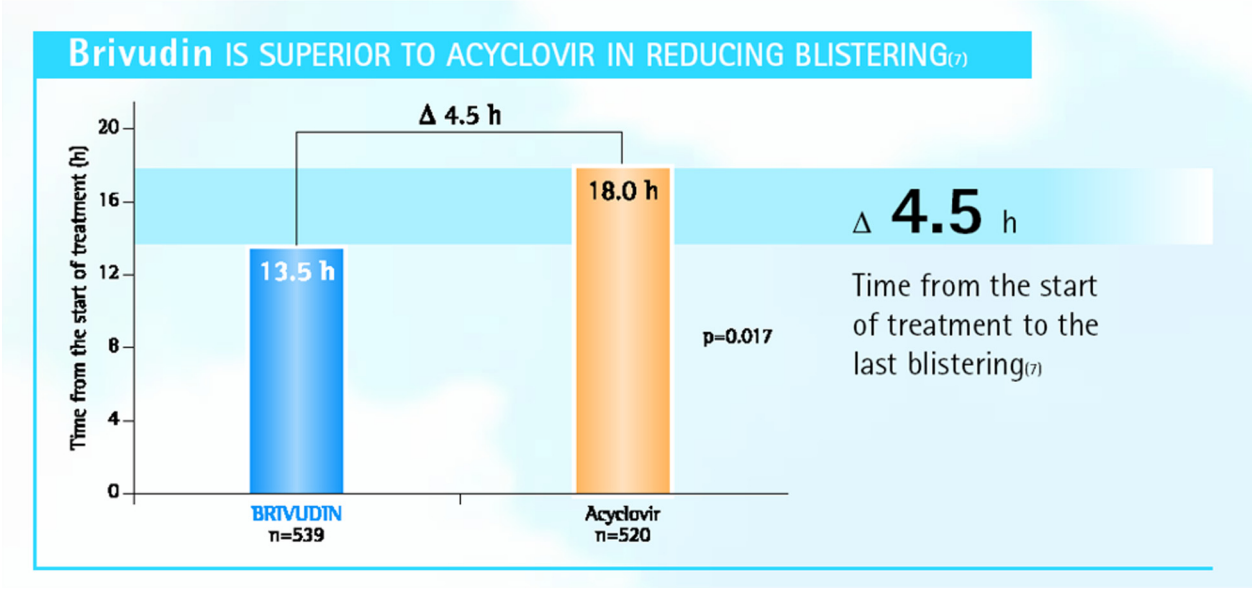

Figure 6. BVDU is superior to acyclovir in reducing the time to blistering[10].

BVDU should not be administered concomitantly with 5-fluorouracil (Fu)

The arabinofuranosyl counterpart of BVDU, BVaraU, is roughly equally or slightly more potent than BVDU[8]. It was administered in Japan for the treatment of herpes zoster in patients. It was thereby ignored, that at the same time, some of these patients were treated concomitantly with 5-fluorouracil (FU) (or a prodrug thereof) for underlying cancer. BVaraU was administered orally, and through the (gastro)intestinal flora degraded to (*E*)-5-(2-brovinyl)uracil (BVU). The latter was taken up in the bloodstream, and inhibited the key enzyme, 5-dihydropyrimidine dehydrogenese (DPD) responsible for the degradation of uracil and analogues thereof,

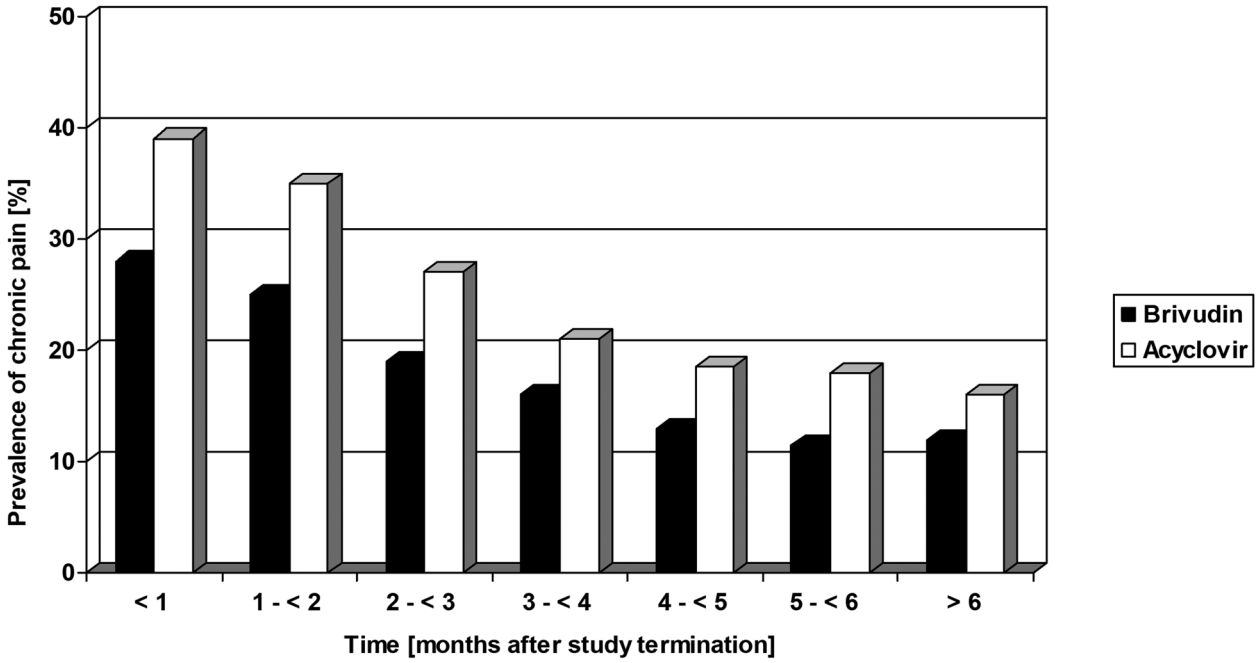

Figure 7. Monthly prevalence of postherpetic pain after termination ($N = 545$) of randomised, double-blind study of oral BVDU (brivudin) at 125 mg once daily versus acyclovir at 800 mg 5 times daily for 7 days ([11]Abstract no. 45).

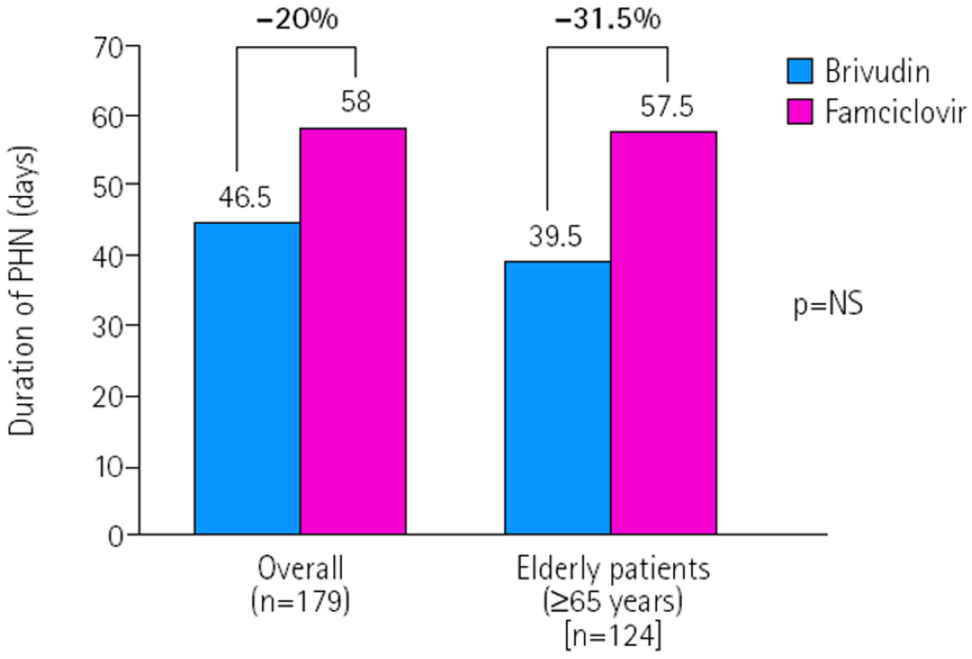

Figure 8. Median duration of post-herpetic neuralgia (PHN) in the overall study population and in the subgroup of elderly patients [12].

such as FU (Figure 9). BVU thus enhanced the plasma levels of FU, resulting in a number of casualties due to the toxicity of FU[8]. Because of this toxicity, BVaraU has not been further developed for the treatment of herpes zoster, although BVaraU was not toxic by itself; and in the absence of FU, BVaraU would obviously not lead to any casualties. This explains why in the prescription of BVDU a warning is included that the compound should not be administered concomitantly with anticancer agents. This warning should be restricted to FU (and prodrugs thereof, such as capecitabine).

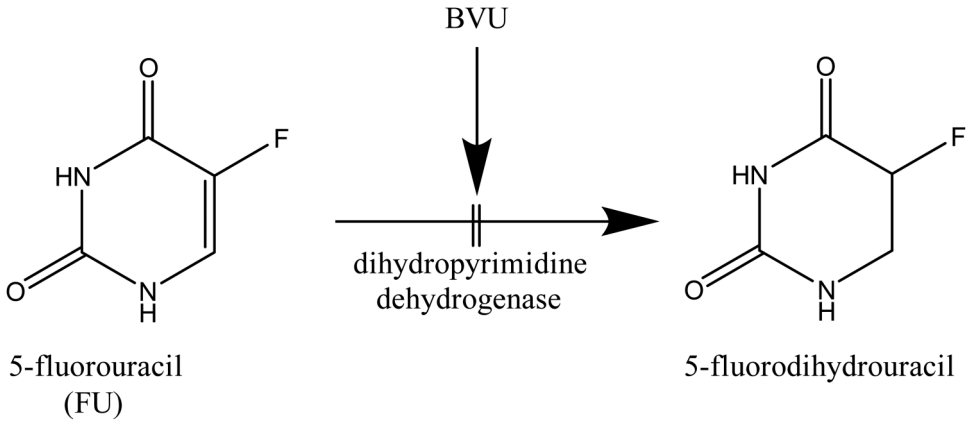

Figure 9. Inhibition of the degradation of 5-fluorouracil by BVU.

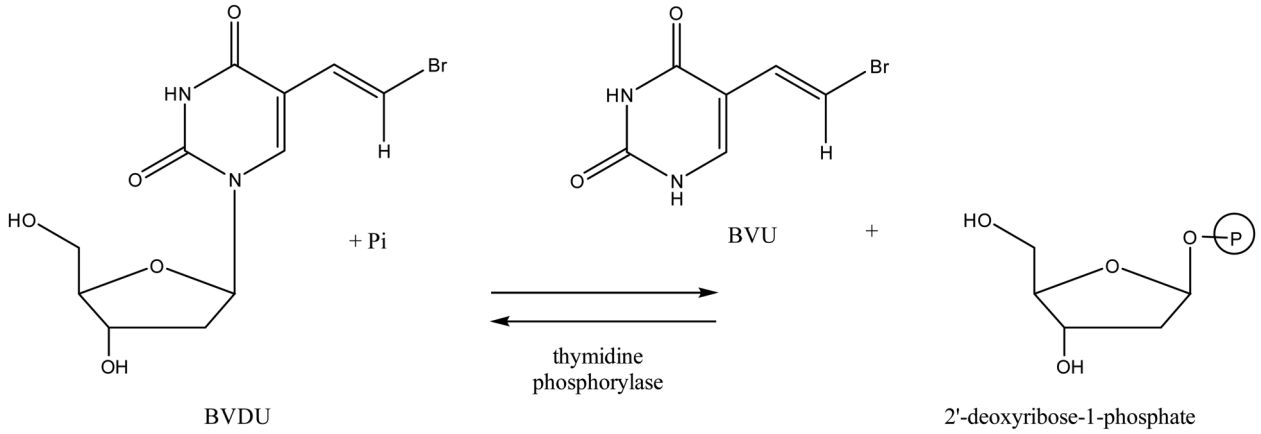

Figure 10. Degradation of BVDU to BVU by thymidine phosphorylase.

However, whether BVDU, through the release of BVU (Figure 10) would result in increased toxicity of FU has never been demonstrated. Following oral administration of BVDU, the compound is rapidly taken up in the bloodstream (assumingly before the (gastro)intestinal flora has the opportunity to degrade it to BVU). When BVDU is transported to the liver, it may be converted to BVU in a reaction that is perfectly reversible (BVDU + Thymine ▢ BVU + 2'-Deoxythymidine)[13], so that the BVU levels generated by BVDU may not be sufficient to exceed the FU toxicity threshold.

Fermavir (Fv-100), prodrug of Cf-1743, a bicyclic nucleoside analogue (BCNA)

Although BVDU is exquisitely potent in inhibiting VZV replication in cell culture, its potency can still be superseded by Cf-1743[14]. A prodrug thereof, the 5'-valine ester, has been developed which is still awaiting phase III clinical trials, before it could be further envisaged for marketing. Unlike BVaraU and BVDU, the BCNA Cf-1743 cannot be converted (by a phosphorylase) to a free base, and, hence, it would not inhibit DPD, thus excluding the possibility of enhancing FU toxicity. The BCNA Cf-1743, FV-100 or any other prodrug of Cf-1743 may represent serious drug candidates for the treatment of VZV infections such as herpes zoster, but whether they would be ever developed (and commercialized) for this purpose can only be guessed upon.

Epilogue

In May 2003, with lectures in Palermo (27 May 2003), Messina (28 May 2003), and Catania (29 May 2003), I made a big tour through Sicily. As my host, Prof. Giovanni Romero took me on a Saturday morning to his home village. He introduced me to his friend, the local pharmacist, thereby explaining (in Italian) that I had discovered a compound that the pharmacist was certainly selling in his own pharmacy, I clarified that the compound concerned was BVDU, used in the treatment of herpes zoster, but this clarification did not satisfy the pharmacist. I then reviewed all possible names known for herpes zoster, including zona, shingles, and varicella-zoster, but all in vain, until my choice fell on what is known in Flemish as 'St

Table 1. List of countries where BVDU is commercially available[15]

Countries	Brand and generic names of BVDU substitutes
Argentina	Zostydol
Austria	Mevir
Belgium	Zerpex
Bosnia and Herzegovina	Virocid
Bulgaria	Brivir
China	Zostex
Costa Rica	Brivox
Croatia	Brivuzost
Czech Republic	Zostevir
Dominican Republic	Brivox
El Salvador	Brivox
Estonia	Brivumen
Georgia	Zolet
Germany	Menavir, Premovir, Zostex
Greece	Brivir, Zostevir
Guatemala	Brivox
Honduras	Brivox
Hungary	Brivustar
Italy	Brivirac, Zecovir
Latvia	Brivumen
Lithuania	Brivumen
Luxembourg	Zerpex, Zonavir
Nicaragua	Brivox
Panama	Brivox
Portugal	Bridic
Poland	Premovir
Romania	Brival
Serbia	Brivuzost
Slovakia	Zovudex
Slovenia	Premovir
Spain	Brinix, Nervinex, Nervol
Switzerland	Brivex
Turkey	Zostex

Antonius vuur', and in Italian as 'Fuego di San Antonio', and now the pharmacist reacted instantly: 'Si signore, we call the compound Brivirac', which he then dug up from his collection. He was so excited that he wanted to celebrate our encounter with a cup of grappa, but this was at 11 am, and I was not accustomed to drinking grappa that early in the morning. He then gave me the whole bottle of grappa, which I took home and savoured during the following weeks. The Italian trade name for BVDU (Brivirac®) (Table 1) has since this Sicilian adventure (and hospitality) remained firmly fixed in my memory.

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