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Antiviral Research 24 (1994) 191–204

Antiviral Research

Interferons in human papillomavirus infections

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(Received 9 December 1993; accepted 14 February 1994)

Abstract

Human papillomavirus (HPV) infections usually present as benign warts (e.g., *condyloma acuminatum*, CA) but can also be responsible for dysplasia and carcinoma. Therapeutic options include chemotherapeutic agents, cryotherapy and surgery, but all these treatments are anti-tumor, not anti-viral. Interferons (IFNs) are the only anti-viral drugs approved for the therapy of benign HPV-related lesions. While IFN-α, IFN-β and IFN-γ have all been tested against CA, most information is available on IFN-α which appears efficacious via a number of routes of administration, schedules and dosages with an acceptable safety profile. The highest rate of success with IFN-α therapy, in terms of reduced recurrence rates of CA was reported from studies in which all visible lesions were surgically removed with subsequent administration of subcutaneous local IFN-α. Less data is available on the efficacy of IFNs in the treatment of HPV-related dysplasia and carcinoma, but combination therapy (e.g., IFN-α plus retinoids for cervical carcinoma) appears promising. Future advances in control of HPV-related lesions are expected to continue to involve IFN combined with non-antiviral therapies as well as the use of exogenous inducers of IFNs and other cytokines.

Key words: Interferon; Human papillomavirus; Genital wart; Interferon therapy

1. Introduction

At least 14 of the more than 70 known types of human papillomaviruses (HPV) are associated with ano-genital lesions. The spectrum of manifestations of ano-genital HPV ranges from subclinical infections to benign warts, abnormal genital cytol-

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SSDI 0166-3542(94)00016-2

ogy and dysplastic lesions to carcinoma. Genital warts, also referred to as venereal warts or condyloma acuminatum (CA), are the most prevalent viral sexually transmitted disease in the United States (Koutsky et al., 1988).

Whereas the need to treat cancer is obvious and the therapy of dysplasia can prevent the development of carcinoma, there are many reasons to treat benign warts such as decreasing disease transmission, relief of symptoms and improvement of cosmesis.

Various criteria help determine the treatment of choice including the histologic grade of the lesion (i.e., benign vs. neoplastic), the size and number of lesions, the history of previous therapy, the clinical appearance and anatomic site of the growth (flat vs. exophytic) and the immune status of the patient. Traditional therapeutic options for neoplasia include surgery, radiotherapy and chemotherapy while surgery (especially using lasers) and cryotherapy are commonly used for dysplastic lesions. Modalities are frequently used for benign tumors (i.e., warts) include topical agents such as podophyllin, podophyllotoxin (Podofilox), 5-fluorouracil, bichloroacetic acid and trichloroacetic acid. Ablative techniques include excisional surgery, electrocautery and laser vaporization as well as cryotherapy. All the preceding treatments for warts are symptomatic in that they may rid the patient of the clinically apparent lesion but not of the viral infection. It is hoped, however, that disruption of the wart may expose viral antigens to the host's immune system thereby activating it to hold latent HPV in check. This theoretical scenario is frequently not 100% efficient at controlling subclinical HPV. Therefore, symptomatic treatment of warts is associated with high rates of recurrence often due to HPV in clinically normal-appearing skin (Ferenczy et al. 1985).

Since no approved vaccine exists for HPV, only one antiviral/immunologic therapy exists for HPV infections, interferon (IFN). IFN alpha (IFN-α), IFN beta (IFN-β) and IFN gamma (IFN-γ) all have been used with vary degrees of success as monotherapy or in combination with symptomic treatment for HPV-associated lesions (Tyring 1987).

Condyloma acuminatum (CA) is a benign tumor of viral etiology in which the replication of HPV depends on the state of differentiation of the epithelium. Genital warts also demonstrate aberrancies of endogenous cytokines, oncogenes and antioncogenes (Arany et al., 1993). Therefore, not only are the antiviral and immunomodulatory activities of IFN important in the treatment of CA, but the actions of IFN on differentiation, cell proliferation and oncogene expression also appear to play a role in the therapy of this disease. IFNs also exert their anti-proliferative effect on HPV infected cells by affecting the expression and phosphorylation of the retinoblastoma tumor suppressor gene via the inhibitory TGFβ_1/IFN-β cytokine pathway (Arany et al. 1994).

2. Clinical trials of interferons for treatment of HPV-associated lesions

Although clinical trials have evaluated a variety of IFN types, only IFN-α3 (natural IFN-α: Alferon, Purdue Frederick, Norwalk, CT) and IFN-α2b (recombi-

nant) (Intron, Schering Plough, Kennilworth, NJ) are currently approved by the US Food and Drug Administration for treatment of CA.

Early attempts to treat anogenital HPV-associated lesions with topical IFN-α (natural) were reported to produce complete response (CR) rates of 90% (36/40 patients) (Ikic et al., 1975b) to 100% (10/10 patients) (Ikic et al., 1975a) with vulvar and vaginal warts. Topical IFN-β (natural) was subsequently studied by a number of other investigators for therapy of CA but with less success. Vesterinen et al. (1984b) reported a 38% (3/8 patients) CR with IFN-β vs. 0% (0/5 patients) with placebo but with a recurrence rate (RR) of 100% (3/3 patients) at 1–2 months. Keay et al. (1988) achieved a 33% (10/30 patients) CR with IFN-α vs. a 29% (8/28 patients) CR with placebo.

Both cervical intraepithelial neoplasia (CIN) and cervical cancer are highly associated with HPV infection. The first reports of topical IFN-α (natural) therapy of CIN were promising: 54% (7/13 patients) CR with IFN-α vs. 0% (0/18 patients) with placebo (Ikic et al., 1981). Moller et al. 1983 reported 50% (3/6 patients) CR with IFN-α but had no placebo group. Byrne et al. (1986) observed a 23% (3/13 patients) CR with IFN-α vs. 23% (2/13 patients) CR with placebo. Yliskoski et al. (1990) reported 44% (4/9 patients) CR with IFN-α for CIN vs. 70% (7/10 patients) CR with placebo. However, no complete responder treated with IFN-α had relapsed at 16 months vs. 29% (2/7 patients) RR following treatment with placebo. Topical recombinant(r) IFN-α2c used for treatment of CIN produced a CR of 67% (6/9 patients) (Schneider et al., 1987). Marcovici et al. (1983) reported 100% (25/25 patients) CR using topical plus intralesional (IL) IFN-β.

The only study of topical IFN for cervical cancer produced 33% (2/6 patients) CR with topical IFN-α (natural) but 11% (1/9 patients) with topical plus intramuscular (IM) IFN-α (natural). No recurrences were noted 11–34 months later.

These investigations demonstrated that topical IFN preparations were well tolerated but produced a wide range of clinical results. No preparation of topical IFN is currently available for clinical use.

Intralesional use of IFNs has been reported from numerous studies. Natural IFN-α used IL for CA produced 50% (5/10 patients) CR (no placebo group) with a 20% (1/5 patients) RR at 3 months in a study reported by Geffen et al. (1984). In the largest study of natural IFN-α used IL for CA, Friedman-Kein et al. (1988) observed 62% (41/66 patients) CR with IFN-α vs. 21% (14/66 patients) with placebo. The RR at 4 months was 25% (9/36 patients) with IFN-α; at 2 months the RR was 23% (3/13 patients) with placebo. Reichman et al. (1988b) reported that the CRs with rIFN-α2b, natural IFN-α and IFN-β used IL were 48% (11/23 patients), 45% (7/15 patients) and 50% (10/20 patients), respectively, vs. 22% (4/18 patients) treated with placebo. At a mean of 46 days 33% of the IFN treated patients (all three groups) experienced a recurrence vs. none of the four placebo treated patients who had cleared. Other studies using IL rIFN-α2b produced the following rates of CR: Eron et al. (1986): 36% (42/116 patients) with IFN-α vs. 17% (20/116 patients) with placebo; Vance et al. (1986a): 28% (9/32 patients) with IFN-α vs. 16% (6/38 patients) with placebo; and Boot et al. (1989): 60% (6/10 patients) with IFN-α (no placebo). The RR of the IFN-α treated patients was reported only from the Eron et

al. (1986) study: 21% (5/25 patients) at 9 months, and from the study of Boot et al. (1989): 17% (1/6 patients) at 2 months. The RR of the placebo treated patients was not reported from these studies.

Promising results of the IL use of IFNs for CIN have been reported with the following CRs: Uyeno (1982): IFN-β, 100% (2/2 patients); Stefanon (1983): IFN-β (IL plus topical), 60% (3/5 patients); DePalo et al. (1984): IFN-β (IL plus topical), 54% (7/13 patients); Hsu et al. (1984): IFN-α (natural), 100% (3/3 patients); Vasilyev et al. (1990): IFN-α (natural), 29% (36/125 patients); Stellato (1992): rIFN-α2b, 33% (8/24 patients); Micheletti et al. (1992): IFN-β, 59% (19/32 patients); and Frost et al. (1990): rIFN-α2b, 11% (1/9 patients). None of these preceding studies of IL use of IFN for CIN were placebo controlled, nor did they document a RR. Choo et al. (1986) observed CR of 86% (6/7 patients) with IL use of IFN-α (natural) for CIN and 40% (2/5 patients) with IL use of IFN-β. At 12 to 24 months the RR with IFN-α patients was 50% (3/6 patients), but no RR was provided for IFN-β treated patients nor was there a placebo group. Dunham et al. (1990) treated CIN with rIFN-α2b (IL) with a CR of 29% (2/7 patients) vs. 0% (0/7 patients) with placebo; no RR data was given. One study of the IL use of IFN-γ for CIN reported a CR of 63% (5/8 patients) vs. 13% (1/8 patients) with placebo (Iwasaka et al., 1990); no recurrences were reported from either group.

Systemic use of IFN can include subcutaneous (SQ) or intramuscular (IM) administration some distance from the lesion. Gall et al. (1985) observed CRs with IM use of natural IFN-α for CA as follows: 1.0 MU (million units/treatment): 43% (6/14 patients); 3.0 MU: 57% (17/30 patients); and 5.0 MU: 69% (11/16 patients). Weck et al. (1988) reported CRs with IM or SQ use of natural IFN-α: 1.0 MU: 21% (6/28 patients) and 3.0 MU: 33% (21/63 patients). No placebo group was used in these studies and no RR was reported. Reichman et al. (1988a) used 1.0 MU or 3.0 MU, IM or SQ for CA producing a CR of 25% (19/77 patients) followed by a RR of 5% (1/19 patients) at 4 months. Olsen et al. (1985) observed that IM use of natural IFN-α (3.0 MU) produced 26% (9/34 patients) CR but with a 44% (4/9 patients) RR at 1 month.

Results with natural IFN-α, IFN-β and IFN-α2b given SQ at 2.0 MU by Reichman et al. (1990) for CA were similar with only a 17% (22/133 patients) CR vs. 10% (4/42 patients) with placebo. The RR was 23% (5/22 patients) with IFN at 176 days vs. 0% (0/4 patients) with placebo at 168 days. A similar low rate of efficacy with SQ use of rIFN-α2a was reported with 3.0 MU as well as 9.0 MU both producing 21% CR (11/53 patients and 12/56 patients, respectively) vs. 18% (10/57 patients) CR with placebo (Condylomata 1991). At 9 months the 9.0 MU group had experienced a 36% (5/14 patients) RR vs. a 9% RR in each of the other two groups. Gross et al. (1986a) reported that rIFN-α2b in SQ doses from 1.5 MU to 18 MU produced CRs ranging from 43% (3/7 patients) to 71% (5/7 patients). At 7 months the RR in both groups was 0%. Using rIFN-α2c SQ at 5.0 MU Gross et al. (1986b) observed a 71% (5/7 patients) CR. Gall et al. (1991) noted that IM use of rIFN-α2a at 3.0 MU produced a 50% (12/24 patients) CR vs. 36% (9/25 patients) CR with IM consensus IFN at 2.5 MU or 5.0 MU. Using 3.0 MU of rIFN-α2b Panici et al. (1989) observed the same 20% CR whether IFN was given IM (10/51 patients) or SQ (10/50 pa-

tients). At 12 months the RR was 10% (1/10 patients) in both groups. Treatment of CA with IM use of IFN-β (2.0 MU) produced a 82% (9/11 patients) CR vs. 18% (2/11 patients) with placebo. No recurrences were noted at 10–12 months in either group.

Studies with systemic use of IFN-γ for CA have also produced variable results. Kirby et al. (1986) reported that CRs with IM use of rIFN-γ ranged from 9% (1/11 patients) with 0.2 to 2.0 MU to 20% (3/15 patients) with 0.2 to 0.5 MU. In 1988 Kirby et al. reported that only 7% (2/28) of patients achieved a CR with rIFN-γ, 0.2 MU given IM. None of 10 patients treated by Zouboulis et al. (1991) experienced a CR with 1.5 MU of rIFN-γ administered SQ. Somewhat better results were seen by Fierlbeck (1987) with rIFN-γ 1.5 to 3.0 MU given SQ which produced a CR of 29% (5/17 patients). The highest rate of CR, 56% (34/61 patients), was observed by Gross et al. (1988b) with rIFN-γ, 0.75 to 6.0 MU given SQ. No recurrences were noted after 7 to 16 months.

Two studies have examined the efficacy of systemic IFN-α for the treatment of CIN. Yliskoski et al. (1991) found no difference in the CRs or RRs with SQ natural IFN-α vs. placebo. On the other hand, Schneider et al. (1987) observed a 20% (1/5 patients) CR with topical plus SQ rIFN-α2c and a 71% (5/7 patients) CR with SQ use of rIFN-α2c. None of these CR patients had experienced a recurrence by 7.5 months.

Most recently a number of investigators have studied the efficacy of IFNs in combination with more traditional cytodestructive therapies for CA. Reports by Schneider et al. (1987), Fierlbeck (1987), Weck et al. (1988) and Erpenbach et al. (1990) combining surgery with IFN-α or IFN-γ were promising, but no RRs were provided for surgery without IFN. Since the visible lesions were removed by surgery, the RR is the primary criterium for determining the efficacy of combination therapy. In the majority of reports providing RRs for both combination treatment and monotherapy groups, however, laser surgery followed by IFN-α was superior to surgery alone. Vance et al. (1990) observed a 19% (5/27 patients) RR at 13 weeks with laser surgery followed by rIFN-α2b vs. 38% (18/47 patients) with laser alone. A similar effect was reported by Hohenleutner et al. (1990): a 42% (8/19 patients) RR at 3 months with laser surgery followed by rIFN-α2b vs. 81% (13/16 patients) with laser alone. Likewise, Peterson et al. (1991) noted a 48% (13/27 patients) RR at 3 months with laser surgery followed by IFN-α2b vs. 77% (17/22 patients) with laser alone. Davis et al. (1992) reported a 21% (3/14 patients) RR at 9.5 months following laser surgery with a single injection of rIFN-α2b vs. 45% (9/20 patients) at 11.5 months with laser alone. Laser surgery followed by rIFN-α2a resulted in a 4% (1/27 patients) RR at 18 months in an investigation by Reid et al. (1992) vs. 38% (3/8 patients) in patients treated only with laser. One study, however, demonstrated no benefit from laser surgery followed by rIFN-α2a, i.e., 68% (48/71 patients) RR at 9 months vs. 61% (39/64 patients) treated with laser alone.

Electrocautery followed by IFN resulted in reduced RRs in two small studies. Piccoli et al. observed that 25% (1/4 patients) experienced a recurrence of CA at 6–12 months after electrocautery followed by rIFN-β vs. 67% (2/3 patients) following electrocautery alone. Tiedemann et al. (1988) noted a 9% (2/22 patients) RR at 6

months with electrocautery followed by rIFN-α2b vs. 45% (5/11 patients) with electrocautery alone.

Interestingly, cryotherapy plus IFN-α did not appear more beneficial than cryotherapy alone in two studies. Handley et al. (1992) found that rIFN-α2a (SQ) followed by cryotherapy of CA resulted in a 50% (8/16 patients) RR at 3 months in contrast to a 38% (6/16 patients) RR with cryotherapy alone. When cryotherapy was followed by rIFN-α2a (SQ) in a study by Eron et al. (1993), 69% (25/36 patients) experienced a recurrence by 6 months vs. a 73% (27/37 patients) recurrence with cryotherapy alone.

Podophyllin has also been combined with IL use of rIFN-α2b (Douglas et al., 1990). The RR with this combination, 67% (22/33 patients) at 40 days, however, was not different than the RR with podophyllin alone, 65% (13/20 patients), at 31 days.

3. Side effects associated with IFN therapy

The "flu-like syndrome" associated with IFN becomes more prevalent with doses above 1.0 MU and start to be problematic with doses above 5.0 MU per treatment. However, interferons are well tolerated by almost all patients who receive doses below 5.0 MU per treatment. This observation is especially true if the patient is forewarned of this possible side effect and is premedicated with 500 mg to 1000 mg of acctaminophen. Similar doses of acctaminophen can be repeated each 4 to 6 h as required. It is frequently useful to administer the first in a series of IFN injections in the late afternoon thus allowing the patient to reach home before any side effects occur. Although a minority of patients may report slight lethergy throughout a series of IFN injections, most persons rapidly develop tolerance to the "flu-like syndrome" after only two or three injections.

Mild to moderate leukopenia and thrombocytopenia as well as minor elevations in serum levels of certain liver enzymes have occasionally been observed in otherwise healthy CA patients receiving IFN in the 1.0 MU to 5.0 MU range. These changes however, have been transient and rapidly reversible. Neutralizing antibodies to IFN-α occasionally develop, but their clinical significance is not completely understood. However, these neutralizing antibodies appear to be more prevalent following administration of recombinant IFN-α than after natural IFN-α (Antonelli et al., 1993; Von Wussow et al., 1987).

The prevalence and severity of IFN-associated adverse events appear dose dependent but not route dependent. In other words, 1.0 MU of IFN-α would be expected to have an equal chance of producing a "flu-like syndrome" whether given IL into a wart or SQ into the arm. The clinical efficacies of 1.0 MU of IFN-α given via these two routes, however, would not be expected to be the same. This difference is perhaps best illustrated by the 2- to 3-fold higher CR of CA observed with rIFN-α2b or natural IFN-α given IL (Reichman et al. 1988b) vs. SQ (Reichman et al. 1990) (in the arm) at the same schedule.

Whereas spontaneous regression of CA has to be considered in any IFN study,

responses to IL administration of IFN may also be due partly to the non-specific inflammatory effects of the injection itself. When the CR rate of placebo-treated patients is subtracted from the CR rate of IFN-α treated patients in the two studies by Reichman et al. (1988b, 1990) noted above, the CR with IL use of IFN-α appears to be more than 3-fold greater than with SQ use of IFN-α. This difference in efficacy implies that the same dose of IFN given locally may produce higher levels of IFN in the CA than when given at a distant site, thus increasing the therapeutic effect. Although the previously sited studies suggest a linear dose response to IFN, this relationship does not appear to be valid at doses above 4–5 MU per treatment. At approximately this point, the therapeutic effect on CA appears to plateau while the incidence and severity of the "flu-like syndrome" increases linearly. Therefore large and/or multiple genital warts are less likely to respond to 5.0 MU per treatment than are moderate numbers/sizes of CA to 2.5 MU.

FDA approval of both rIFN-α2b and IFN-αn3 for treatment of CA was based in IL studies. While IL use of IFN-α does appear more efficacious for an individual lesion than does systemic use of IFN-α, there are limitations as to how many lesions can be treated (or the patient will allow to be treated) per visit. Most patients will accept a few IL treatments with IFN, especially if a small volume of fluid and a 30 gauge needle are used and if the patient has CA refractory to or recurrent after cytodestructive therapy. Systemic IFN therapy would probably be more acceptable both to the patient and to the physician, but most reports indicate that SQ or IM use of IFN-α produce only mild to moderate rates of CR.

4. Factors affecting clinical response to IFNs

The wide range of CRs with systemic use of IFNs may reflect a multitude of variables such as the type of IFN, the dose and the schedule of administration. Many studies using systemic IFN for CA do not state if the IFN was injected into the arm or into an area closer to the lesions (e.g., suprapubic or upper inner thigh). While it has not been definitively proven that "regional" systemic therapy is more efficacious than "distant" systemic treatment, the two Reichman et al. studies (1988b, 1990) previously quoted suggest this possibility.

Numerous patient variables may influence the response to IFN given via any route. The immune status of the patient appears very important. Douglas et al. (1986) documented the lack of efficacy of IFN-α in patients infected with the human immunodeficiency virus. A variety of other immunocompromising diseases as well as drugs may depress the response to IFN. For example, cigarette smoking has been associated with a higher incidence of CA and an increased rate of malignant transformation and may therefore have an adverse effect on the response to exogenous IFN (Daling et al. 1986). Other variables that may adversely affect the response to IFN include perianal location of warts, CA present for over a year and/or resistant to, or recurrent, following other therapies, CA containing HPV types 16 and/or 18 as well as dysplastic or malignant lesions (Byrne et al., 1986; Schneider et al., 1987; Vesterinen et al., 1984). Furthermore, IFN therapy may not be appropriate

in some clinical settings. For example, IFN should not be used in pregnant patients due to its anti-proliferative activity. IFNs are relatively contra-indicated in organ transplant patients due to reports of increased rates of rejection (Kovarik et al., 1988). Therapy with IFN has also been reported to exacerbate certain autoimmune diseases (Ronnblum, 1991).

5. Antiviral therapy vs. antiwart therapy

Cytodestructive and chemotherapeutic (topical) treatments for CA have several advantages such as being rapid in their actions. This advantage is especially true for surgical treatments since the effect is immediate. The disadvantages of such therapies include immediate pain and persistent discomfort with cryotherapy and with acids. Surgical techniques require anesthesia, produce bleeding and can result in secondary infections and possibly scarring. The primary disadvantage of such treatments is that they only remove the obvious lesions and do not have any direct benefit on latent HPV. Therefore cytodestructive techniques are frequently associated with high rates of recurrences of CA. Cytodestructive techniques, however, are standardly used as first line therapy for CA because they are often less expensive (with the exception of laser surgery) and require less visits than a course of IFN.

Therapy with IFN, however, offers the antiviral/immunomodulatory activity that can affect latent HPV thereby reducing the recurrence rate. Although IFN therapy is occasionally associated with a mild "flu-like syndrome", the major disadvantage of its use is that 4 or more weeks of twice or thrice weekly therapy may be required to clear moderate sizes/numbers of CA. Large (multiple cm^3) lesions usually do not clear with IFN monotherapy. The logical and practical choice for CA that is resistant to, or recurrent following, cytodestructive therapy is to combine the antiviral/immunomodulatory activities of IFN with the anti-wart properties of traditional therapy. In theory the advantages of such combinations would be rapid clearance of the CA with a reduced recurrence rate. Other than the occasional mild "flu-like syndrome" following the first injection(s) of IFN, the disadvantages of such combinations should equal those of the cytodestructive method chosen. Since surgical treatment of CA removes the tumor at the beginning of therapy, the only criterium for evaluating surgery plus IFN is the recurrence rate. Initial debulking of the tumor (CA) would be expected to remove the clinically abnormal tissue as well as some of the virus. In addition, removing the tumor helps decrease the source of local immune suppression.

6. Optimizing combination therapy

In seven studies in which the CA were removed either via laser surgery or by electrocautery and the patient then treated with IFN via the IM or SQ route, the RR in patients treated with combination therapy was significantly less than with ablative monotherapy (Piccoli et al., 1989; Tiedemann et al., 1988; Vance et al.,

1990; Hohenleutner et al., 1990; Peterson et al., 1991; Davis et al., 1992; Reid et al., 1992). Only one such combination study has failed to demonstrated beneficial effects on the RR by IFN (Condylomata 1993). A multitude of variables previously discussed may affect the RR following combination therapy. In addition, a delay of more than a day between excision of CA and initiation of IFN could allow unwanted HPV replication, thus increasing the RR. Not all of the successful combination studies report the area of the body where the SQ or IM injection was given. In the report of Reid et al. (1992) the rIFN-α2a (1.0 MU/treatment) was given SQ adjacent to the site of the excised CA. The injections were continued 3 times a week for at least 10 weeks. Interestingly the trial demonstrating no added benefit from combination therapy (Condylomata 1993) employed the same IFN (rIFN-α2a) at a 3-fold higher dose (3.0 MU/treatment). The patients in the latter study, however, received IFN in the arm, and injections were conducted 3 times a week for only 4 weeks. Whether the site of injection and/or the length of IFN therapy determined the marked reduction in RR with the Reid et al. (1992) study is unknown.

A cytodestructive therapy less expensive and more readily available than laser surgery or electrocautery would be ideal for combination therapy with IFN. Cryotherapy would appear to be useful in such combinations due to its low cost and its potential to expose viral antigens to the host's immune system. Surprisingly, however, the two reports of cryotherapy plus rIFN-α2α demonstrated no reduction in RR vs. cryotherapy alone (Handley et al. 1992; Eron et al., 1993). Likewise, rIFN-α2b plus podophyllin did not further reduce the RR observed with podophyllin monotherapy (Douglas et al., 1990).

Therefore, the ideal combination therapy for large and/or numerous CA appears to be surgical excision followed immediately by SQ, local administration of IFN-α. Whether injections need to be continued 3 times a week for at least 10 weeks as in the study by Reid et al. (1992) should be determined by further studies.

The usual patient with a moderate number/size of treatment-resistant or recurrent CA may not necessitate the expense and morbidity associated with surgery. These patients can effectively combine self-treatment with podophyllotoxin (podofilox 0.5%) solution with SQ local administration of IFN-α (e.g., in the suprapubic area/inguinal folds). A patient with CA can master self-administration of IFN with no more difficulty than diabetics learn to give themselves insulin. Ideal patients for such home combination therapy are those persons who are healthy other than having CA and whose pretreatment complete blood count and liver and kidney function tests are within normal limits. Such patients could then be seen in the clinic after approximately 1 month (or sooner if complications develop or the CA clear before 1 month). Although this home combination therapy plan (or variations thereof) is effective (personal observation) and is gaining acceptance, no published study has yet documented its efficacy and cost-effectiveness.

An ongoing combination trial for CA at the University of Texas Medical Branch compares the efficacies and toxicities of IFN-α vs. IFN-γ vs. IFN-α plus IFN-γ. Further investigations are needed to determine the therapeutic index of other possible combinations (e.g., retinoids) with IFN with attention to IFN dosage, schedule and route.

7. Future of IFNs in HPV infections

Although no topical IFN preparation is generally available, clinical trials are ongoing with topical inducers of IFNs (and of other cytokines) such as imiquimod (Spraunce et al., 1993). Unless a safe and effective vaccine for HPV becomes available, the logical and practical future for IFN therapy (exogenously produced or endogenously induced) appears to be in combination therapy so as to produce a rapid disappearance of the tumor (CA) and a reduced RR.

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