ORIGINAL PAPERS

IS ACUTE MUCOSITIS A DOSE LIMITING FACTOR IN ALTERED FRACTIONATED RADIOTHERAPY ?

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Received 25 May 1997; revision received 12 March 1998; accepted 20 March 1998.

There is now a substantial number of studies on the radiotherapy for head and neck cancer using altered fractionation schedules, and nearly all prove an increased incidence and severity of acute mucosal reactions. Thus, when one considers alternative fractionation strategies, acute mucosal reactions become the most significant dose-limiting regardless of radiation quality because mucosa is very sensitive to the accumulated dose per week (AD) and each of these schedules involves a higher AD than that in conventional treatment [Peters et al, 1991; Thames et al. 1990; Withers et al, 1989]

Clinical data selection

Incidence and kinetics of acute and late radiation effects in normal tissues are discussed based on the analysis of 25 clinical data sets taken from the literature [Ang, 1990; Dische, 1981; Fletcher et al, 1962; Horiot et al,1988; Horiot et al, 1992; Johnson et al, 1992; Kaanders et al 1992; Knee et al, 1985; Karin et al, 1987; Lamb et al, 1990; Maciejewski et al, 1995; Maciejewski et al, 1991; Marcial et al, 1987; Moez et al, 1984; Nguyen et al 1985; Olmi et al, 1990; Parsosn et al 1998; Peracchia and Salti, 1981; Saunders et al, 1991; Svoboda 1984; Van der Schueren et al, 1990; Wang et al, 1985; Wang 1988; Wendt et al 1989]. The raw data were available for a few studies, but in most cases data were taken from reports in the literature.

RESULTS AND DISCUSSION

Accumulated dose/week (AD) vs incidence and severity of acute mucositis

In conventional radiotherapy given in 1.6-2.0 Gy fractions up to a total dose of about 70 Gy, confluent mucositis (CM) is generally reached at day 22. The threshold for the CM appears to be around 20 Gy and the CM usually develops about 9 days after delivering that dose. However, some studies suggest that the onset of CM may depend on the accumulated dose/week and the larger AD is the sooner CM is reached.

All these observations suggest that the intensity of acute epithelial reactions, and likely other H-type-like tissues reflect the balance between the rate of cell killing by irradiation and the rate of regeneration of the surviving stem cells. Once a critical level of survival cells has been attained, a certain type of clinical damage will develop at a rate only determined by the cellular kinetics of the tissue. When a peak in the CM is reached, further stem cell killing cannot produce an increase in the intensity of acute reactions, but could be manifested as prolonged time to heal the reactions. In the Van der Schueren [Van der Schueren E. et al, 1991] study a splitcourse irradiation was used, and even concentrated multiplefractions per day (MFD) schedules (Tab.I Scheme I-III)

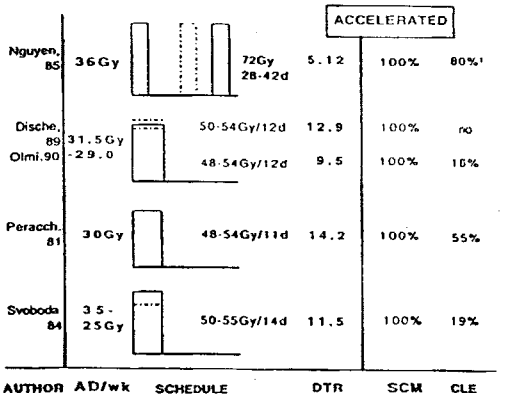

Table I. Incidence of confluent mucositis (SCM) and consequential late effects (CLE) in accelerated fractionation. (AD/wk - accumulated dose per week; DTR - Dose-Time Ratio)

with a high AD did not change the time and rate of the CM development and did not produce prolonged confluent mucositis; in fact the duration of CM was shorter than in conventional treatment, and they healed completely during 2-3 week breaks in the treatment.

Accelerated and hyperfractionated schedules

The analysis of the sets of data of accelerated, predominantly accelerated and hyperfractionated radiation treatments shows that, except for hyperfractionation and short single course accelerated regimens, the AD is not constant in consecutive weeks of treatment. High AD, above 25 Gy is typical for accelerated treatments when the dose is condensed into a single course in a short overall treatment time. In concomitant boost schedule [Ang et al, 1990; Peters et al, 1991] a high AD of 16.5 Gy is delivered either in each of the first or/of the last two weeks of treatment and in the remaining weeks it is not higher than 9 Gy. In double-BID-split course schedule [Van der Schueren et al, 1990; Wang et al, 1985] the AD of 16 Gy is given in the first 2.5 weeks and in the last 1.5 week separated by 2-3 weeks break. In so-called escalated fractionation [Kaanders et al, 1992; Maciejewski et al, 1992] the AD increases from 14-15 Gy to 18 Gy in the last two weeks of 5-week treatment.

It seems that it is not easy or even impossible at least for some schedules to express the AD for a given treatment with a single value, and this could have an important impact on the onset and intensity of confluent mucositis. For that reason, an additional factor: Dose-Time Ratio (DTR) was introduced in the analysis. In general, it is the ratio of Dose Intensity (DI=D/T), and then it can be written as

$$DTR = dN/T / / T/N = dN^2/T^2$$

where: DTR is an average dose/day x average fractions/day and it is quantified in Gy/day^2. For 60 Gy in 30 fractions during 42 days, and for 70 Gy in 49 days the DTR is equal 1.02 Gy x day^{-2}.

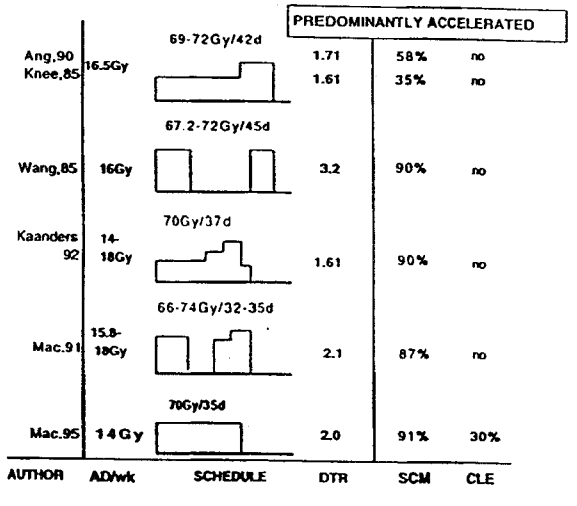

Table II. Incidence of confluent mucositis (SCM) and consequential late effects (CLE) in predominanty accelerated fractionation.(AD/wk - accumulated dose per week; DTR - Dose - Time Ratio)

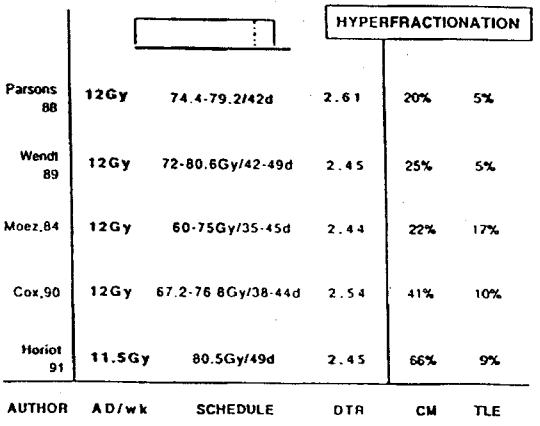

Table III. Incidence of acute mucositis (CM) and true late effects (TLE) in hyperfractionation.
(AD/wk - accumulated dose per week; DTR - Dose - Time Ratio)

For hyperfractionated treatments (tab.III) where the DTR was in the range of 2.44-2.61 Gy/day^2 and the AD was about 11-12 Gy the incidence of confluent mucositis was between 22% and 60%. For predominantly accelerated treatments (Tab.II), an increase of the AD to 14-18 Gy, even when DTR was in similar range as for hyperfractionation, leads to the increased incidence of CM, in the range from 58% to 91%. Drastic reduction with the treatment time to 9-14 days in purely accelerated treatments resulted in the AD above 25 Gy, and the DTR in the range 5014 Gy x day^{-2} producing presistent confluent mucositis in 100% of patients.

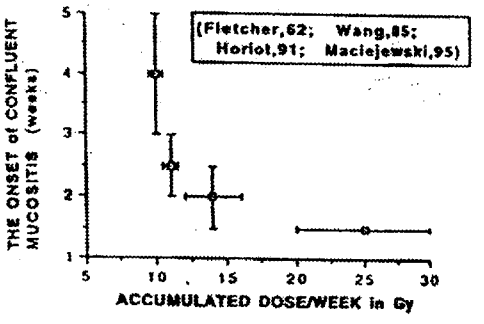

Figure 1. The onset of confluent mucositis depending on accumulated dose per week.

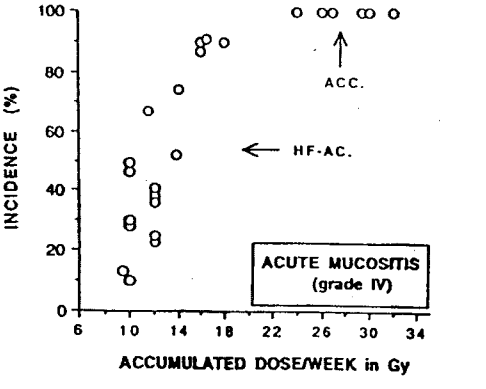

Figure 2. Incidence of confluent mucositis depending on accumulated dose per week.

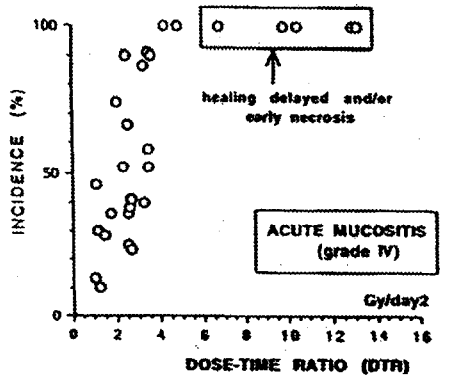

Figure 3. Incidence of confluent mucositis depending on Dose-Time Ratio.

Figure 2 and Figure 3 show that both the accumulated dose/week (AD) and the Dose-Time Ratio (DTR) correlate with the incidence of severe confluent mucositis (CM). It has to be pointed out that if the AD is higher than 20 Gy and the DTR increases above 6 Gy/day^2 healing of the CM was always delayed and consequential late necrosis has often occured as a consequence of severe epithelial denudation. If in the irradiated area epithelial stem cells are deeply or completely depopulated, and the healing, if it occurs, is delayed, infection and/or trauma can lead to secondary damage to subjacent normal tissues and this type of necrosis occurs as a consequence of a severe acute reaction. A typical example of this phenomenon in of 55% cases of non-healing confluent mucositis leading to mucosal
necrosis was observed by Peracchia [Perachcia et al, 1981] after 50-54 Gy delivered in 9-11 days of accelerated treatment. For this treatment the AD was 30 Gy and the DTR was 14.2 Gy x day^{-2}.

Suprisingly, typical consequential necroses in 30% of patients were observed by Maciejewski et al [Maciejewski et al, 1995] when 70 Gy in 35 fractions (1 daily fraction) was delivered in 35 days (7days per week treatment) instead of 49 days. Although the AD was 14 Gy and the DTR was as low as 2.0 Gy/day^2 , soft tissue necrosis or osteoradionecrosis occured.

Oral mucosa classified as rapidly proliferating tissue is capable of compensating for cell killing induced by 1.8 Gy/day towards the end (probably not the begining) of a 6-week treatment. The cells surviving an irradiation of oral mucosa are likely to rapidly lose any latent damage and react as if they had not been irradiated. They probably need very little time for recovery and when the subsequent irradiation is given no cumulative effects are seen [Van der Schueren et al, 1990]. This suggestion mainly comes from the studies when the AD was high but only for a short period of 1-2 weeks and it was followed by low AD (10 Gy) in consecutive weeks or was separated by a 2-3 week break. Seven-day treatment without weekend-breaks, even when conventional fraction of 2 Gy was repeated in 24-hour intervals, led to an unacceptable risk of consequential effects. It seems that constant AD of 14 Gy through out 5 consecutive weeks of treatment could make cell proliferation not effective enough to compensate for radiation cell killing. In consequence, gradual denudation of epithelial stem cells resulted in early necrosis which occured 2-10 months after the treatment.

Assuming that the TRU (tissue rescuing unit) for mucosa is 1 stem cell per 1/10cm^2 area to avoid persistent confluent mucositis and consequential necrosis [Withers et al, 1988], the observed effects in 30% case of early mucosal necrosis may suggest that cell survival was on average less than 7 cells per 1 cm^2. Thus, only less than 7/10 of the given dose was effectively compensated for by repopulation of mucosal stem cells which may suggest D_{profil} of about 1.1-1.2 Gy per day, which is less than the value generally assumed for conventional fractionation of 70 Gy given in 5-day treatment.

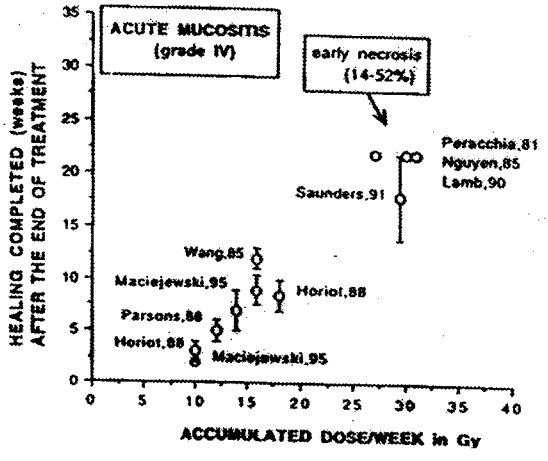

Figure 4. The time of complete healing of confluent mucositis depenging on accumulated dose per week.

If more than 7 stem cells per 1 cm^2 of mucosa survive irradiation and/or migration of epithelial cells from the periphery is not affected by infection or trauma, it seems that the time of the complete healing of acute mucositis depends on the AD (Fig.4). If the AD is higher than 14 Gy complete healing can even be prolonged to 20 weeks after treatment.

CONCLUSIONS

When fractionation regimens are altered to achieve a therapeutic gain through an increased tumour response relative to late normal tissue response, acute mucosal reactions become dose limiting in radiotherapy for head and cancer.

An acceptable risk of acute mucositis can be expected when the Dose-Time Ratio (DTR) is

lower than 2.5 Gy x day -2 and the accumulated dose per week (AD) is less than 12 Gy. Higher AC can only be considered if it is administered in no more than 2 consecutive weeks of 5-6 week treatment or a 2-3 week split is given between series of high AD (or DTR).

A high constant value of the AD (>14 Gy) during 5-6 weeks of treatment or the AD above 20 Gy and DTR above 10 Gy x day-2 lead to a high risk of persistent confluent mucositis and consequential late necrosis which may occur within 4-8 months after treatment.

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