Review

Potential of Amifostine for Chemoradiotherapy and Radiotherapy-associated Toxicity Reduction in Advanced NSCLC: A Meta-Analysis

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Abstract. *Background/Aim: The addition of amifostine to chemoradiotherapy (CRT) or radiotherapy (RT) in advanced, inoperable NSCLC presents varying toxicity. The present study examined amifostine's effect on toxicity and efficacy of CRT or RT alone. Materials and Methods: Database searches yielded 16 eligible trials comprising of 1,057 patients. Results of randomised trials were pooled and used to estimate the overall effect. Results: Amifostine reduced the risk of >grade 2 acute oesophagitis by 26% [risk ratio (RR), 0.74; 95% confidence interval (CI)=0.65-0.86; p<0.0001] and the risk of acute pulmonary toxicity by 44% (RR, 0.56; 95%CI=0.41-0.75; p=0.0001). Risk of complete response was unchanged (RR, 1.64; 95%CI=0.99-2.73; p=0.06), partial response was unchanged (RR, 0.92; 95% CI=0.73-1.16; p=0.48). Statistical heterogeneity was high for toxicity but low for response. Conclusion: Statistical heterogeneity of retrived results casts doubt over amifostine's efficacy in this setting, despite decreased acute oesophageal and pulmonary toxicity. Amifostine did not compromise treatment efficacy.*

The standard-of-care for locally advanced, inoperable non-small cell lung cancer (NSCLC) is chemoradiation therapy (CRT) (1); concurrent CRT (conCRT) affords maximum survival when contrasted with sequential CRT (seqCRT) or radiation therapy (RT) alone (1). However, conCRT does not necessarily improve the therapeutic ratio as it is associated with significant, particularly oesophageal, morbidity (1, 2) and increased treatment mortality (1). Therefore, conCRT is generally reserved for patients with a good performance status and limited co-morbidities (1); geriatric patients are often denied conCRT due to these factors or a belief that they are inherently more vulnerable to conCRT morbidity (3). A meta-analysis of the Radiation Therapy Oncology Group (RTOG) experience found that a higher biologically effective dose (BED) provided improved loco-regional control and overall survival in the setting of CRT (4), however, morbidity remained an issue (4). Therefore, morbidity of conCRT for NSCLC may impede improvements in tumour control or survival for these patients by preventing radiation dose escalation or causing treatment interruptions, where often survival is poor, even with conCRT. The use of amifostine (Ethyol, WR-2017), a cytoprotective agent, has been investigated in this setting in multiple phase II and III randomised and non-randomised trials (RCTs and non-RCTs) however questions remain regarding the efficacy and safety of amifostine in this setting.

Amifostine is an organic thiophosphate pro-drug that is de-phosphorylated *in vivo* into its active moiety, WR-1065(5). Concerns regarding its selectivity for normal tissue have hampered its use and widespread recommendation by consensus groups such as the American Society for Clinical Oncology (ASCO), despite many small trials showing favourable results for treatment efficacy end-points. Therefore,

the present review expands previous meta-analyses (6-8) that have suggested the safety and efficacy of amifostine in this setting to give a more comprehensive view of the role of amifostine in the treatment of patients with inoperable NSCLC treated with CRT or RT alone.

Materials and Methods

Search strategy for identification of studies. MEDLINE (accessed through PubMed), EMBASE and the Cochrane library were searched. Reference lists of relevant studies were searched to identify further relevant studies.

Type of studies. Eligible studies were either RCT or non-RCT types.

Type of participants. Eligible trials included patients with histologically-confirmed advanced, medically- or surgically-inoperable NSCLC treated exclusively with CRT or RT alone. Trials were included if some, but not all, patients have had previous treatment.

Type of interventions. Eligible trials employed amifostine as a cytoprotectant. Trials were included where amifostine was not the sole intervention of interest but comprised part of the intervention.

Type of outcomes. Eligible trials reported acute or late treatment-related toxicities or a measure of CRT or RT efficacy, although both were preferable.

Primary Outcomes: 1) Incidence and severity of acute treatment-related toxicity (various toxicity scales); 2) Incidence and severity of late treatment-related toxicity (various toxicity scales); 3) Amifostine-related toxicity.

Secondary Outcomes: 1) Response Rates; 2) Survival Data.

Statistical analysis. Forest Plots were generated for acute oesophageal and pulmonary toxicity; data regarding other acute side-effects were too heterogeneous to include. The threshold for acute oesophageal toxicity was ≥Grade 2, where possible. No threshold was required for acute and late pulmonary toxicity due to heterogeneity in reporting. Complete and partial response were also analysed. Toxicity and response was considered dichotomous endpoints and Mantel-Haenszel (M-H) test used for comparison. The Chi-square test was used to test for statistical heterogeneity for each comparison, the I^2 statistic quantified statistical heterogeneity. Only RCTs were included in statistical analysis due to the potential for increased reporting and selection bias (24).
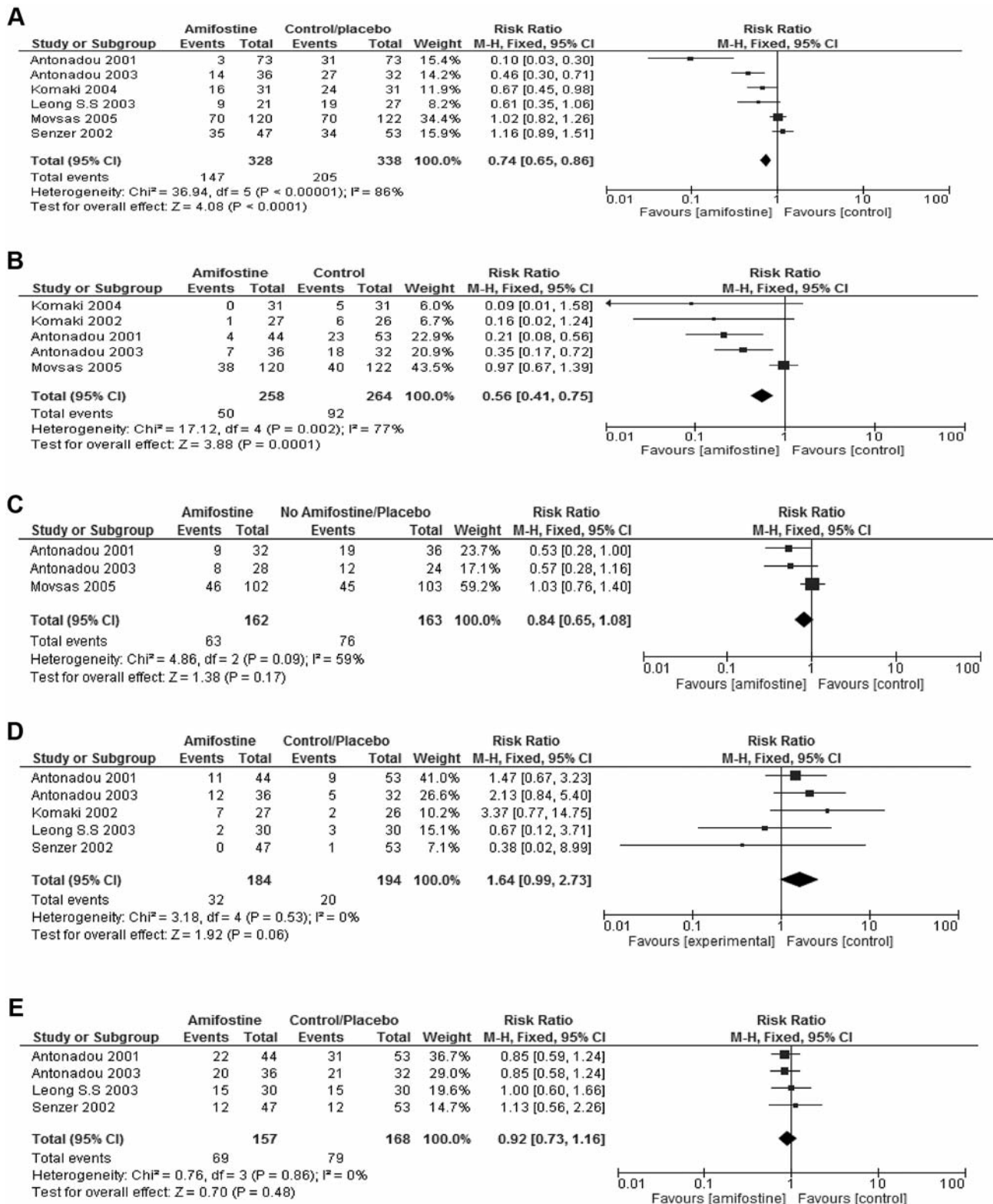
Results

Description of studies. Thirteen full-text articles comprised of 7 RCTs with one long-term follow-up study and 6 non-RCTs, one of which was a non-randomised controlled clinical trial. One RCT was a double-blind trial. A further 3 studies only available in abstract form were added, as their full texts were not available and efforts to obtain the full texts from corresponding authors were unsuccessful. Overall, 16 studies involving 1,057 patients were included in the present review.

Risk of bias in included studies. The evident biases in included studies include publication bias, selection bias, chronology bias, confounding and outcome reporting bias. Study publication bias may have resulted in overestimation of amifostine efficacy. Selection bias existed where trials incorporated performance status and age into their eligibility criteria (9-16, 20-22). Chronological bias may have been a factor in one trial using a historical control (22); bias may have been introduced due to changes in protocol, practices or procedures following the treatment of the control group. Confounding bias existed where trials failed to control for factors affecting outcome. Outcome reporting bias was prevalent across many studies reporting various toxicity assessments, responses and survival outcomes. Comparison between studies was, therefore, difficult. Only articles available in full text were suitable for quality analysis. RCTs scored from 19-25 (9-15) and non-RCTs scored from 13-17 (16-18, 20-22). Statistical power was analyzed separately; power was not calculated for 7 non-RCTs (16-18, 20-22). Seven RCTs were powered for toxicity end-points alone. One RCT did not document power calculations (15), four RCTs did not meet their power calculations for toxicity end-points (9, 11, 13, 14).

Effect of interventions. Six RCTs indicated a significant decrease in the severity of acute oesophageal toxicity in the amifostine arm (9, 10, 12, 13, 15, 25). RTOG98-01 reported no statistically significant difference in two physician-rated end-points (10). One RCT noted no statistically significant difference in favour of amifostine (11), while another RCT found similar incidence and severity between arms (14). Non-randomised trials reported varying incidence and severity of acute oesophageal toxicity for various outcomes (16-18, 20-22, 26). Two non-RCTs reported similar incidence and severity of oesophagitis in patients with or without amifostine (16), while another noted no statistically significant difference in favour of amifostine when compared to a historical control (22).

Pooling results for 6 RCTs (9-12, 14, 15) identified that compared to placebo or no amifostine, amifostine significantly reduced the risk of ≥grade 2 acute oesophageal toxicity by 26% (Risk Ratio (RR), 0.74; 95%Confidence Interval(CI)=0.65-0.86; $p<0.0001$). Three RCTs were excluded from the analysis; data were not available in full from two (25, 27); another did not record acute oesophageal toxicity (13). Statistical heterogeneity was evident (Chi-square=36.94, df=5, $p<0.00001$; I^2=86%) (Figure 1A). Four RCTs recorded statistically significant decreases in incidence of acute pulmonary toxicity, reporting on various toxicity outcomes (9, 12, 13, 15). One RCT did not analyze differences in incidence and severity of acute pulmonary toxicity in a statistical manner (10), finding a similar incidence of grade 1-5 toxicity (10). Three non-RCTs reported similar incidences of pulmonary toxicity (17, 21, 22). One non-RCT found a similar incidence

A

Study or Subgroup	Amifostine Events	Total	Control/placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	3	73	31	73	15.4%	0.10 [0.03, 0.30]
Antonadou 2003	14	36	27	32	14.2%	0.46 [0.30, 0.71]
Komaki 2004	16	31	24	31	11.9%	0.67 [0.45, 0.98]
Leong S.S 2003	9	21	19	27	8.2%	0.61 [0.35, 1.06]
Movsas 2005	70	120	70	122	34.4%	1.02 [0.82, 1.26]
Senzer 2002	35	47	34	53	15.9%	1.16 [0.89, 1.51]
Total (95% CI)		328		338	100.0%	0.74 [0.65, 0.86]
Total events	147		205			

Heterogeneity: Chi² = 36.94, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.08 (P < 0.0001)

B

Study or Subgroup	Amifostine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Komaki 2004	0	31	5	31	6.0%	0.09 [0.01, 1.58]
Komaki 2002	1	27	6	26	6.7%	0.16 [0.02, 1.24]
Antonadou 2001	4	44	23	53	22.9%	0.21 [0.08, 0.56]
Antonadou 2003	7	36	18	32	20.9%	0.35 [0.17, 0.72]
Movsas 2005	38	120	40	122	43.5%	0.97 [0.67, 1.39]
Total (95% CI)		258		264	100.0%	0.56 [0.41, 0.75]
Total events	50		92			

Heterogeneity: Chi² = 17.12, df = 4 (P = 0.002); I² = 77%
Test for overall effect: Z = 3.88 (P = 0.0001)

C

Study or Subgroup	Amifostine Events	Total	No Amifostine/Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	9	32	19	36	23.7%	0.53 [0.28, 1.00]
Antonadou 2003	8	28	12	24	17.1%	0.57 [0.28, 1.16]
Movsas 2005	46	102	45	103	59.2%	1.03 [0.76, 1.40]
Total (95% CI)		162		163	100.0%	0.84 [0.65, 1.08]
Total events	63		76			

Heterogeneity: Chi² = 4.86, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.38 (P = 0.17)

D

Study or Subgroup	Amifostine Events	Total	Control/Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	11	44	9	53	41.0%	1.47 [0.67, 3.23]
Antonadou 2003	12	36	5	32	26.6%	2.13 [0.84, 5.40]
Komaki 2002	7	27	2	26	10.2%	3.37 [0.77, 14.75]
Leong S.S 2003	2	30	3	30	15.1%	0.67 [0.12, 3.71]
Senzer 2002	0	47	1	53	7.1%	0.38 [0.02, 8.99]
Total (95% CI)		184		194	100.0%	1.64 [0.99, 2.73]
Total events	32		20			

Heterogeneity: Chi² = 3.18, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)

E

Study or Subgroup	Amifostine Events	Total	Control/Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonadou 2001	22	44	31	53	36.7%	0.85 [0.59, 1.24]
Antonadou 2003	20	36	21	32	29.0%	0.85 [0.58, 1.24]
Leong S.S 2003	15	30	15	30	19.6%	1.00 [0.60, 1.66]
Senzer 2002	12	47	12	53	14.7%	1.13 [0.56, 2.26]
Total (95% CI)		157		168	100.0%	0.92 [0.73, 1.16]
Total events	69		79			

Heterogeneity: Chi² = 0.76, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)

Figure 1. *Forest Plots for comparison: A: acute oesophageal toxicity (grades ≥2), B: acute pulmonary toxicity (all grades), C: late pulmonary toxicity (all grades), D: complete response, E: partial response. M-H: mantel haenszel, CI: confidence interval, df: degrees of freedom.*

of dyspnea grade 4 in patients with and without amifostine pre-treatment (16).

Pooling results from 5 RCTs (9, 10, 12, 13, 15) showed that compared to no amifostine, amifostine reduced the odds of acute pulmonary toxicity by 44% (RR, 0.56; 95%CI=0.41-0.75; p=0.0001). RCTs were not included if acute toxicity was not recorded (11, 14) or if sufficient information was not available (25, 27). Statistical heterogeneity was evident (Chi-square=17.12, df=4, p=0.002; I^2=77%) (Figure 1B).

Eleven trials recorded acute haematological toxicity, reporting various toxicity outcome measures (9-12, 16-18, 20-22, 26). One RCT found a statistically significant difference in favour of amifostine (12); two RCTs noted no significant difference in favour of amifostine (9, 11); in one no statistical tests were performed, but similar incidences and severity in both arms were reported (10). Non-RCTs reported conflicting incidence and severity of neutropenia (17, 18, 20, 21, 26) and anemia (18, 21) the incidence of thrombocytopenia was low in three non-RCTs (17, 20, 21). One non-RCT reported similar incidence in patients with and without amifostine (16).

Three RCTs assessed other toxicities with no statistical analysis; similar incidence and severity of neurotoxicity (10, 11), nausea, vomiting, diarrhea, constipation (10, 11), alopecia, fatigue (11) cardiovascular, constitutional symptoms, dermatological toxicity, stomatitis, dysgeusia, hepatic toxicity, and pain were noted (10), with no difference in the incidence or severity of non-oesophageal toxicities between the arms (14). Non-RCTs reported varying incidences of palmar-plantar erythrodysesthesia (17, 18) dermatological toxicity (17, 18) and similar incidence of renal toxicity (18, 20) and neurotoxicity (18, 21); nausea (20), fatigue and fever (21). One non-RCT found similar incidence and severity of hepatic toxicity and alopecia (16).

Eight trials reported late toxicity, predominantly pulmonary toxicity with varying outcome measures. A statistically significant difference in favour of amifostine was found in late pneumonitis (9) compared to no pneumontis (21). Fibrosis incidence varied (9, 15, 17), one RCT found a statistically significant difference in favour of amfostine (27). One non-RCT found no incidence of soft tissue, cardiac or neurological late toxicity (18). RTOG 98-01 noted no significant difference in the incidence of non-pulmonary toxicity at initial (10) and 10 years follow-up (19).

Pooling the data for 3 RCTs (9, 10, 15) identified that amifostine compared to no amifostine does not reduce the risk of late pulmonary toxicity (RR, 0.84; 95%CI=0.65-1.08; p=0.17). Six RCTs did not record late pulmonary toxicity or did not provide sufficient data (11-14, 25, 27). Statistical heterogeneity was noted (Chi-square=4.86, df=2, p=0.09; I^2=59%) (Figure 1C).

Eleven trials administrated amifostine intravenously (IV) (9-15, 17, 18, 20, 22) and four subcutaneously (16, 18, 21, 25). Doses and scheduling varied greatly in different trials. Four RCTs reported a significantly increased incidence of hypotension of varying incidence and severity in the amifostine arm (10-13); others did not statistically compare arms but reported greater hypotension incidence in the amifostine arm. Three non-RCTs reported hypotension with amifostine (18, 20, 22); one during IV administration only (18). One RCT and two non-RCTs reported no hypotension (17, 21, 25).

Nausea or emesis was reported in 9 trials; (9-11, 15, 17, 18, 20, 21, 25). One RCT noted a significantly higher incidence (10); others did not statistically compare arms, but noted greater nausea and/or emesis in the amifostine arm (9, 11, 15, 25). Three non-RCTs and one RCT noted alterations in planned amifostine administration and refusal due to nausea/emesis (20, 25), reduced mean dose of amifostine (17), cessation of amifostine (21). Other toxicities such as dysgeusia (12) sneezing (11, 12), dizziness, chills and hiccups (11) occurred significantly more frequently in the amifostine arm. Fatigue, local pain, erythema, asthenia, fever and rash were also noted (17, 18, 20, 25).

All trials analyzed response and/or survival as surrogates for treatment efficacy. Response was most frequently analyzed using a Computed Tomography (CT) scan following treatment completion (9, 11, 14-18, 20, 21). Response and survival differences were non-significant between both arms of RCTs (9-13, 15, 25); similar response rates were noted between both arms in one RCT (14). Long-term follow-up of RTOG98-01 noted non-significant differences in response or survival (19). There was a trend towards greater complete response in one RCT (13).

Five RCTs (9, 11, 13-15) were statistically analyzed for complete response; four RCTs (10, 12, 25, 27) were excluded as response data were not available. Amifostine increased the risk of complete response compared to no-amifostine or placebo (RR, 1.64; 95% CI=0.99-2.73; p=0.06). Statistical heterogeneity was evident (Chi-square=3.18, df=4, p=0.53; I^2=0%) (Figure 1D).

Pooling partial response results for 4 RCTs (9, 11, 14, 15) showed that amifostine compared to no amifostine or placebo did not alter the odds of partial response (RR, 0.92; 95%CI,=0.73-1.16; p=0.48). Partial response results were insufficient or missing for five RCTs (10, 12, 13, 25, 27) Statistical heterogeneity was low (Chi square=0.76, df=3, p=0.86, I^2=0%) (Figure 1E).

Non randomised trials reported varying rates of response and survival end-points (16-18, 20-22, 26).

Discussion

Conflicting guidelines are pronouncely reflected in the results of this study, regarding acute and late treatment-related toxicity. American Cancer Society guidelines endorse

amifostine to reduce acute oesophagitis (28), citing only one study (included in this study) (12). ASCO guidelines (2008) cite insufficient data to recommend amifostine in the same setting (29).

Our results suggest that amifostine can almost halve the odds of ≥grade 2 acute oesophageal toxicity, with considerable heterogeneity. Another meta-analysis (7) agrees with amifostine's ability to reduce oesophageal toxicity incidence, specifically dysphagia, although the trials included were not NSCLC trials. The results agree with two reviews supporting amifostine's potential to reduce incidence and severity of acute pneumonitis (30, 31).

I^2 values for acute oesophageal, acute pulmonary and late pulmonary toxicity, respectively, indicate considerable and substantial statistical heterogeneity (24). Heterogeneity stems largely from clinical and methodological variations between included studies.

Generally, acute toxicity incidence and severity was greater in RCTs using conCRT (9-13), compared to RT alone (15), as expected. Incidence and severity of acute and late toxicities were similar in patients treated with hyperfractionated and conventional regimens; rates of late pulmonary toxicity in both hypofractionated regimens (17, 21) were similar and slightly lower compared to those of conventional fractionation, as expected (17).

Amifostine protocol varied significantly between trials. The best and worst amifostine protocols in terms of efficacy could not be established due to considerable heterogeneity. Reducing time between administration and RT to ≤15 min offers better cytoprotection (33). Six trials adhering to this reported varying incidence of acute and late toxicities, suggest that other factors are relevant (9, 11, 14-16, 20). Compliance varied; 29% of patients completed amifostine per protocol, covering 40% of weekly RT in RTOG98-01 (10). Amifostine may not have been present in sufficient frequency or quantities to mediate clinically relevant cytoprotection, possibly explaining failure to establish significance for two acute oesophageal toxicity end-points (10). This argument is weakened by another RCT's positive results administering a similar amifostine protocol, also covering 40% of fractions(12), although adherence was not reported (12).

Generally, there was greater incidence and severity of acute and late treatment-related toxicity in RCTs compared to non-RCTs; non-RCTs gave more regular doses of amifostine and higher overall doses (ranging from 500-1,000 mg/m^2); suggesting a benefit to higher doses of amifostine more regularly, although the use of vastly different treatment regimens in non-RCTs may have contributed to variations. However, late toxicities did not correlate with a difference of 500 mg in some trials (10, 17, 18, 21). Two RCTs reported significantly reduced acute treatment-related toxicities when altering dose based on body surface area (9, 15), a later trial achieved statistically similar results with a flat dose (12).

Generally, treatment-related toxicity incidence and severity was similar in trials giving daily (9, 17, 18) (one non-RCT was an exception with no late pulmonary toxicity (21)) and more irregular amifostine (10, 13), further contributing to difficulty establishing the optimum amifostine regimen. Subcutaneous administration was associated with lower severity of acute oesophageal and no late pulmonary toxicity in one non-RCT (21), contrasting with others using a combination or IV administration. Subcutaneous administration is more commonly associated with reducing amifostine-related toxicity (32). Therefore, it appears that higher overall doses of amifostine given >15 min before treatment may mediate better cytoprotection, although it is difficult to establish a clear relationship due to heterogeneity of amifostine protocols used.

Only two trials positive for acute toxicity reduction had sufficient statistical power to detect a clinically relevant difference in acute oesophageal toxicity (10, 12); possibly accounting for varying incidence and severity of acute toxicity among under-powered trials. Sufficiently powered trials were also conflicting. Amifostine was a component of the intervention in four non-RCTs (17, 18, 21, 26); therapy in these trials differed from the standard-of-care (34). Varying chemotherapeutic agents and doses contributed to varying haematological toxicities.

Confounding factors affecting oesophagitis incidence and severity such as Nodal stage (N) 2 disease (35) and pre-existing dysphagia (35) were not recorded in many trials, therefore contributing to methodological heterogeneity. Smoking status (36) was reported in one trial. Tumour in the upper lobe combined with diabetes mellitus or chronic lung diseases (31), poor pre-RT pulmonary function (31), plasma transforming growth factor-beta 1 (TGF- β1) ratio of ≥1 pre- or post-RT (31) and other biochemical markers (30) increase the risk of pneumonitis and subsequent fibrosis. Tumour location, co-morbidities and plasma TGF-β1 were not recorded, pre-treatment pulmonary function tests were completed by two studies (12, 20).

The majority of patients were males, showing Irish (37) and international (38) incidence patterns. No patient had previous surgery, while some non-RCTs included patients who had prior chemotherapy (17, 18, 21), which may have contributed to clinical heterogeneity. Most patients had a good performance status and minimal weight loss; many trials incorporated performance status into eligibility criteria (9-16, 20-22), limiting the opportunity for patients with significant co-morbidities to participate, although for such patients conCRT may be contraindicated due to significant morbidity; they are under-represented in trials of CRT for advanced stage, inoperable NSCLC (3, 4), however the majority of patients diagnosed with lung cancer in Ireland are >65 years (37). Frail patients or those unable to tolerate conCRT, may be offered seqCRT or RT alone (39), although one RCT

treating with RT alone had patients with minimal weight loss and a good performance status (15).

The optimal amifostine administration protocol is unclear (40). Individual's tolerance to amifostine varies with age, performance status, gender and tumour type (40). Toxicity results were reported together and toxicity varied despite patient populations being similar in terms of the above factors. Varying administration protocol contributed to methodological heterogeneity (40).

Amifostine administration protocol affected amifostine toxicity. Subcutaneous administration trials reported no hypotension (18, 21, 25); comparing favourably with IV administration (9-15, 17, 20, 22), this is also supported by others (2, 5, 32). Incidence and severity of other toxicities were reduced with subcutaneous administration. One study used both methods; it noted less amifostine-related toxicity on days where amifostine was administered subcutaneously (18). The subcutaneous route was well-tolerated compared to IV; its applicability to a busy department and its simplicity compared to IV administration have been noted (25) and it has been proposed to increase compliance in relation to RTOG 98-01 (32). Incidence of hypotension and other toxicities varied in trials using IV administration; possibly from variations in monitoring, prophylaxis and patient factors. A dose relationship was apparent; trials reduced dose based on amifostine toxicities experienced: two (17, 21) used an algorithm to individualize doses (40). Other factors including scheduling and frequency of administration were difficult to separate to ascertain their effect on the incidence and severity of amifostine toxicity.

Most trials did not report what time-point the reported toxicity score referred to; the maximum grade, median grade or final grade, contributing heterogeneity to toxicity results. Use of abstracts only for three trials (25-27) meant their contribution was limited and quality analysis not possible. Two trials included other sub-groups and cancer types (15, 25); it was not possible to isolate results for NSCLC for these trials (15). Two acute toxicity end-points could not be incorporated into forest plots for one RCT (10), and no threshold severity of acute and late pulmonary toxicity contributed to statistical heterogeneity.

No evidence of a tumour-protective effect was noticed in survival or response results, concurring with smaller meta-analyses (6-8). The results of one meta-analysis suggest any effect of amifostine on reducing overall response is no larger than a 3% relative risk reduction (6); our results concur with this; the effect on complete response, if any, is no larger than 1%, however, the effect of potential on partial response is larger at 27%, although this result was non-significant it may be important to consider during the informed consent process prior to commencement of amifostine (41).

The potential for tumour protection by amifostine remains a significant barrier to routine use (7) as anti-oxidants can theoretically affect all tissues (41). No RCT included in this review was sufficiently powered to detect small differences in survival between arms; a major reason for opposition to amifostine (32). It has been suggested that cumulative evidence of RCTs should be sufficient proof of absence of tumour protection (42), and that an RCT with adequate power to detect small differences in survival or response requires over a thousand patients per arm which is a waste of limited resources (32, 42). In some cohorts eliminating the possibility of tumour protection may be secondary to improving the therapeutic index as the tumour protective effect is less important (32), this may be relevant for patients included in this review; prognosis is often poor, even with conCRT.

Economic evaluation indicates a favourable cost/utility ratio for amifostine use in ovarian cancer (43) and head and neck (44) cancers; implying amifostine's ability to reduce the need for toxicity management and supportive care. An analysis in NSCLC found amifostine not cost-effective, although this article was only available as an abstract (45). Cost benefit of amifostine in the short-term (the mean follow-up time for the head and neck study was 5.5 months) (44) may be offset by increased recurrence or tumour progression due to tumour protection.

The role of amifostine in routine clinical practice is unclear due to statistical heterogeneity. Future trials should focus on clinical and methodological homogeneity to minimize statistical heterogeneity to give more reliable data prior to routine clinical use. Standardisation is required across toxicity end-points, scales, evaluation and reporting, treatment regimens, populations and amifostine protocols and response evaluation. Long-term follow-up periods, similar to RTOG 98-01, are required to confirm on long-term survival or response effect. The combined effect of amifostine and modern RT techniques (3D-CRT and intensity-modulated RT) should also be investigated. There appear to be no current trials being conducted in this area.

Conclusion

This review expands on smaller meta-analyses; amifostine appears efficacious for acute oesophageal and pulmonary toxicity reduction when administered to patients receiving CRT or RT alone for advanced-stage, inoperable NSCLC. However, the results for both end-points are inconsistent, due to high statistical heterogeneity. The optimum amifostine protocol for maximal efficacy is a result unclear. Subcutaneous administration appears to reduce amifostine-related toxicity. Amifostine does not appear to alter response rates or survival after CRT or RT alone. Further clinical data are required to determine wherther Amifostine should be routinely administered in patients with advanced NSCLC treated with radiotherapy.

Conflicts of Interest

Both Authors have no competing interest to disclose.

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