Support Care Cancer (1998) 6:144–154

ORIGINAL ARTICLE

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Use of mesna to prevent ifosfamide-induced urotoxicity

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Abstract The purpose of this study was to make evidence-based recommendations regarding the mode, dosage and schedule of delivery of concomitant mesna (sodium-2-mercaptoethanesulfonate) to protect against ifosfamide-induced uroepithelial toxicity. A critical review of the literature from 1966 to 1996 was undertaken on mesna administration via the intravenous, oral, or combined modality routes. Outcome measures of urinary symptoms and macrohematuria were emphasized, since these endpoints of urotoxicity are most clinically relevant. The quality of evidence obtained from published clinical research was evaluated based on guidelines developed by the Canadian Task Force on the Periodic Health Examination. Recommendations are now made according to the strength of available evidence on the proper usage of mesna as a protective agent against ifosfamide-induced urotoxicity. There is good evidence that the use of mesna significantly reduces urinary symptoms of dysuria and frequency, as well as the incidences of macrohematuria and microhematuria, when administered concurrently with any dosage of ifosfamide regardless of tumor site. Mesna, given intravenously or orally, is superior to standard prophylaxis with vigorous hydration and alkalinization of urine. A commonly used schedule of intravenous mesna involves a dose equal to 60% of the total ifosfamide dose, divided into three aliquots and administered at 0 h, 4 h and 8 h after ifosfamide. Combined oral and intravenous mesna delivered in some tested schedules is equivalent to intravenous mesna alone, but the optimal schedule and dosage of combined formulation have not yet been established. There is fair indirect but no direct evidence that oral mesna alone is equivalent to intravenous mesna or combined modality use. Further research issues, such as patient compliance with oral mesna and other routes of mesna delivery, are discussed. Ongoing study in the appropriate use of mesna is needed to maximize its value as a uroprotective agent in the clinical setting.

Key words Ifosfamide · Mesna · Urotoxicity · Dose · Schedule

Introduction

Ifosfamide is an oxazaphosphorine alkylating agent with a broad spectrum of antineoplastic activity. It has demonstrated therapeutic efficacy in multiple malignancies including testicular cancer, small-cell and non-small-cell lung cancer, soft tissue sarcoma, gynecological cancer, bladder cancer, non-Hodgkin lymphoma and advanced breast cancer. It is a prodrug requiring in vivo activation by the hepatic cytochrome P450 mixed-function oxidase enzymes, beginning with hydroxylation at the carbon-4 position of the oxazaphosphorine ring [1]. The resultant 4-hydroxy-ifosfamide exists in equilibrium with its acyclic tautomer, aldo-ifosfamide. Aldo-ifosfamide spontaneously decomposes to form ifosfamide mustard, the probable primary alkylating agent, and acrolein. Acrolein has very little antitumor activity, but is highly irritant to the urothelium, and it is therefore believed to be primarily responsible for the urotoxic effects of ifosfamide. In addition to this metabolic step, enzymatic deactivation to 4-keto-ifosfamide or carboxy-ifosfamide from 4-hydroxy-ifosfamide and aldo-ifosfamide, respectively, may occur. These two deactivation products do not have any cytotoxic activity. A further, but reversible, detoxification takes place when 4-hydroxy-ifosfamide reacts with sulfhydryl groups of either proteins or amino acids resulting in the formation of 4-thio-ifosfamide. The slower rate of ring hydroxylation with ifosfamide than with cyclophosphamide leads to a substantial increase in alternative pathway metabolism. Enzymatic oxidation and subsequent *N*-dealkylation of the chloroethyl side chain yields dechloroethyl-ifosfamide and chloroacetaldehyde. Chloroacetaldehyde structurally resembles chloral hydrate and is most probably associated with the neurotoxic effects of ifosfamide [1–4].

Mesna (sodium-2-mercaptoethanesulfonate) is a thiol compound that functions as a regional detoxificant of urotoxic ifosfamide metabolites such as acrolein, 4-hydroxy-ifosfamide, and chloroacetaldehyde. After entering the circulation, mesna is oxidized by ethylenediaminetetracetic acid-inhibitable constituents to dimesna, which is then excreted by the kidneys [5]. Between 30% and 50% of glomerularly filtered dimesna is reduced back to mesna in the renal tubular epithelium by glutathione reductase. The resulting free sulfhydryl groups of mesna can combine directly with the double bond of acrolein, or with other toxic oxazaphosphorine metabolites in the bladder to form stable and nontoxic compounds [6]. Figure 1 is a schematic representation of the inactivation of ifosfamide toxic metabolites by mesna [7].

Mesna is highly water soluble and has very little tissue penetration. It is readily excreted by the kidneys, with the result that it is concentrated in close apposition to the urothelium. Rapid urinary mesna excretion leads to a reduction in plasma mesna concentration, allowing detoxification of ifosfamide to occur regionally in the urinary tract. The nonurinary toxic effects and more importantly, the systemic cytotoxic activity of ifosfamide are not attenuated by concomitant mesna [1]. Mesna has a short plasma half-life compared with that of ifosfamide, necessitating its repeated administration to provide continuous adequate prophylactic protection of the bladder.

Mesna can be administered via oral or intravenous routes. Following oral administration, mesna has a

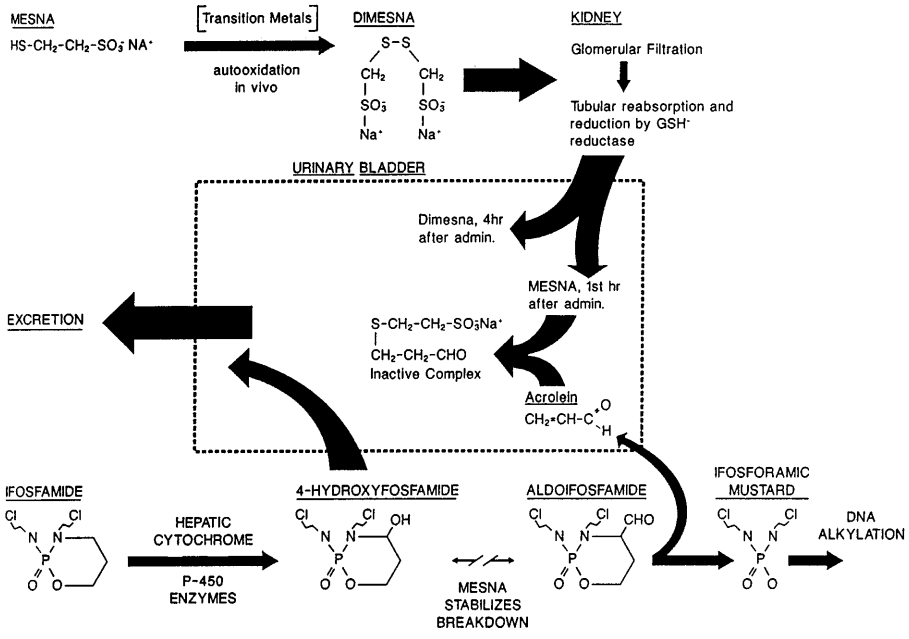

Fig. 1 Schematic representation of inactivation of ifosfamide toxic metabolites by mesna in the urinary bladder. (Reproduced with permission) [7]

bioavailability of between 50% and 75% [1]. Urinary mesna concentrations are approximately half those observed after intravenous infusion, suggesting that doses should be doubled for oral administration. Peak mesna concentration is achieved about 1–4 h after oral ingestion [5, 6]. Urinary excretion of mesna is almost complete in the first 4 h after intravenous administration, but continues for at least 8 h after oral dosing. This is due to delayed absorption from the gastrointestinal tract [1, 6].

Process and methods

Literature review

A computerized literature search was performed, using Medline, for relevant articles in English published from 1966 to 1996. Key words included MeSH terms "mesna" and "ifosfamide." Other sources included manual searches of bibliographies and recent issues of key journals.

Level of evidence

The Canadian Task Force on the Periodic Health Examination [8] was used to evaluate the quality of evidence obtained from published clinical research. The highest level of evidence, level I, was obtained from at least one properly randomized controlled trial. Level II-1 evidence was obtained from well-designed controlled trials without randomization. Level II-2 evidence was derived from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. Level II-3 evidence was obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category. Level III evidence was based on the opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Classification of recommendations

The strength of recommendations to include or exclude a maneuver was graded on a 5-point scale adapted from the Canadian Task Force on the Periodic Health Examination [8]. Grade A recommendation was based on good evidence regarding the inclusion of the maneuver. Grade B recommendation was based on fair evidence supporting inclusion of the maneuver. Grade C recommendation was based on poor evidence for the advisability of including the maneuver, but recommendations may be made on other grounds. Grade D recommendation was based on fair evidence regarding the exclusion of the maneuver. Grade E recommendation was based on good evidence supporting exclusion of the maneuver.

Prophylactic maneuvers to reduce urotoxicity

Prophylactic maneuvers undertaken to prevent ifosfamide-induced urotoxicity have included oral water intake, intravenous hydration, diuretics, urinary alkalinization, bladder irrigation with *N*-acetyl-L-cysteine, indwelling catheters, and oral ascorbic acid. Forced hydration and diuresis with or without alkalinization ensure a substantial urine output, thereby reducing the concentration of the urotoxins and the time they remain in contact with the bladder mucosa. The contribution of urine alkalinization to the efficacy of hyperhydration is not clear. High-volume bladder irrigation also dilutes the toxins and reduces their mucosal contact time. Sulfhydryl group-containing agents such as *N*-acetyl-L-cysteine (NAC) have been used both intravesically and systemically. Intravesical instillations only protect bladder epithelium and tubular damage still occurs, while systemic administration reduces not only the urotoxicity, but also the tumoricidal efficacy of ifosfamide [9]. None of these measures has demonstrated superiority over mesna in the prevention of hemorrhagic cystitis [9–11].

Effectiveness of mesna treatment

A review of 48 clinical studies [12–59] examining ifosfamide either as a single agent or as part of a multidrug chemotherapeutic regimen demonstrates the universal use and therapeutic efficacy of mesna against hemorrhagic cystitis for different tumor sites. There was no evidence to suggest that mesna offers selective uroprotection for any specific tumor type. Mesna was administered concomitantly with ifosfamide in a variable range of dosages, regimens and formulations. Intravenously administered mesna was given in a fractionated dosing schedule of intermittent bolus injections or as a continuous infusion. Specific guidelines on dose requirements and schedule of delivery reed to be established.

Outcome measures

To evaluate the effectiveness of mesna, the primary outcome measures examined were urinary symptoms and macrohematuria, since these are the most clinically relevant. Patients' subjective symptoms of dysuria, frequency and feeling of residual urine were also noted.

Macrohematuria was defined as the presence of more than 50 red blood cells (rbc) per high-power (400′ magnification) field (hpf) in the early morning specimen, or the presence of gross blood or clots in urine. In studies where the incidence of "hemorrhagic cystitis" was reported as the outcome, it was considered as a combination of the above end-points. In studies where the grading criteria of urotoxicity was not specified, grade 3 and 4 toxicities were arbitrarily taken as being clinically important.

Microhematuria was defined as the presence of 5–50 rbc per hpf in the urine, detected by urinalysis and/or urine microscopy. The occurrence of microhematuria was examined, but as its clinical significance is considered minor it did not influence guideline decisions.

Phase III trials of intravenous mesna versus placebo/no treatment

There are at least three randomized studies in the literature comparing the preventive efficacy of mesna and/of placebo/no treatment for ifosfamide-induced urotoxicity [60–62]. The best evidence comes from a placebo-controlled, double-blind study by Fukuoka et al. [60], in which 101 patients with advanced primary or secondary lung cancer being treated by single-agent ifosfamide therapy were randomly assigned to mesna or placebo. Of the 101 patients enrolled in the study, 91 were available for data analysis, 10 were excluded because of poor performance status, pre-existent hematuria, and/or ifosfamide discontinuation due to non-urinary related side effects. Forty-five patients were randomized to mesna, while 46 patients were allocated to placebo. The authors stated a priori that at least 31 patients per arm were thought necessary to demonstrate a statistical significance ($\alpha = 0.05$, detection power 0.8). All patients received ifosfamide by 10- to 15-min intravenous drip administered infusion at a daily dose of 2 g/m^2 for 5 consecutive days. Mesna or placebo was intravenously administered immediately after, and 4 h and 8 h after ifosfamide infusion, for 5 consecutive days. The mesna dose corresponded to 60% of the ifosfamide dose, given in three divided doses daily. End-point measures included micturition pain, feeling of residual urine, and hematuria. Evaluations were conducted every day during the period from the initiation to 2 days after the completion of ifosfamide administration, and abnormal findings were followed until they disappeared or were normalized. Outcome criteria were clearly defined by the authors. Micturition pain and feeling of residual urine graded as severe or moderate were not observed for the mesna group, but were observed for the placebo group with incidences of 19.6% (9/46) for micturition pain ($P = 0.0003$) and 15.2% (7/46) for feeling of residual urine ($P = 0.0009$). The incidence of hematuria graded as severe (gross hematuria) or moderate (>50 rbc/hpf) was 6.7% in the mesna group, and 32.6% in the placebo group ($P = 0.0008$). The "number needed to treat" (NNT) to prevent one event can be calculated as 5 for micturition pain, 6.6 for feeling of residual urine, and 4 for severe or moderate hematuria. This study was well conducted and provides level I evidence [8] supporting the routine concomitant use of intravenous mesna with ifosfamide.

The two other studies addressing this issue were smaller, crossover trials of mesna versus no treatment [61, 62]. Using the POWER sample size calculation program for 2 independent groups [63], assuming the probability of event in the control group to be 30%, and in the mesna group to be 5%, then about 40 patients per arm are needed to demonstrate a statistical significance ($\alpha = 0.05$, power = 0.8). If the groups are related in which each observation in one group can be matched to a corresponding observation in another group, such as in crossover designs, a different calculation method is required (W. Taylor, personal communications, 1981). The null hypothesis claims that mesna is neither better nor worse than no treatment and thus will be preferred 50% of the time; and the alternate hypothesis claims that mesna is better and thus will be preferred more often than no treatment. Therefore, if one desires an 80% chance of detecting a true difference in which either regimen is preferred by at least 75% of the patients, then 29 patients are needed in a crossover study for a two-tailed α s 12 of 0.05.

In the study by Sakurai et al. [61], high-dose ifosfamide infused over 30 min at 6 g/m^2 with or without mesna was administered to 13 patients with advanced non-small cell lung cancer. A randomized crossover, single-blind design was used. Patients received mesna at a dose equal to 60% of the ifosfamide dose, given in three equal aliquots intravenously at 0 h, 4 h and 8 h post ifosfamide infusion. Outcome criteria for frequency and dysuria, macrohematuria, and microhematuria were not defined. Although a statistically significant difference was not observed in the incidence of frequency and dysuria between the patients treated with and without mesna (50% versus 80%), the trend favors mesna use. Only 1 patient treated with mesna developed macrohematuria, compared with 7 when mesna was not administered ($P < 0.025$).

In the study by Bryant et al. [62], ifosfamide at 2 g/m^2 by intravenous bolus with or without mesna was administered to 8 patients with advanced bronchogenic carcinoma. A randomized crossover, single-blind design was also used. Patients received mesna at a dose equal to 60% of the ifosfamide dose, given in three equal portions intravenously, at 0 h, 4 h and 8 h after ifosfamide infusion. Outcome criteria for end-point measures were not defined. No statistical comparisons

were described by the authors. Using Fisher's exact test to calculate *P*-values based on the data described, no significant differences in urinary symptoms, macrohematuria and microhematuria were seen.

The above two studies are both very small, and thus do not possess the power to detect a statistically significant difference when it really exists. These studies are considered as level II-1 evidence [8] because of their small sample sizes, low statistical power, and methodologic flaws such as the lack of properly defined outcome criteria.

Intravenous mesna versus standard prophylaxis/acetylcysteine

There are at least two studies in the literature comparing mesna against standard prophylaxis in the prevention of ifosfamide-induced urotoxicity [10, 11]. Scheulen et al. [10] performed a clinical phase II study in which 151 patients with various refractory malignant tumors were treated with intravenous ifosfamide at 60 mg/kg per day for 5 consecutive days. Altogether, 490 courses of chemotherapy were administered. Among these, 92 were given with conventional prophylactic measures consisting of continuous infusion of 3–4 l of normal saline daily plus alkalinization of the urine with citric acid–citrate complexes. Others received intravenous mesna at a dose of 60% of the ifosfamide dose, given in three divided boluses at 0 h, 4 h and 8 h after ifosfamide. A preliminary analysis done after 248 courses revealed a significantly lower frequency of urinary tract complications in the mesna prophylaxis group. Thereafter, continuation of standard prophylaxis in half of the subsequent patients in the study was not justified, and all patients received mesna prophylaxis. Although criteria for hemorrhagic cystitis were not defined, it was observed in 27% of chemotherapy courses (25/92) in the standard prophylaxis group, versus 4% of chemotherapy courses (16/398) in the mesna group, reaching statistical significance ($P < 0.001$). The flaws of this study include its method of treatment group allocation, since randomization was not mentioned, and there was no evidence for blinding in its outcome assessment.

In another similar but smaller study by Scheef et al. [11], 20 patients with various tumor types received intravenous single-agent therapy with either ifosfamide at 60–100 mg/kg per day for 3–5 consecutive days ($n = 16$) or cyclophosphamide at 44–50 mg/kg per day on 1 day ($n = 4$). Eleven patients were randomized to receive intravenous mesna at a dose of 51–198% of the oxazaphosphorine dose, given in three divided doses at 0 h, 4 h and 8 h after ifosfamide or cyclophosphamide. Nine patients were randomized to receive standard prophylaxis consisting of fluid intake of about 4 l per day, administration of furosemide, and alkalinization of the urine with citric acid–citrate complexes. Macrohematuria was not clearly defined, and the authors did not provide any statistical comparisons. Using Fisher's exact test to calculate *P*-values based on the data described, macrohematuria, defined as greater than 50 rbc/hpf, was observed in 88.9% of patients (8/9) in the standard prophylaxis group, versus 0% of patients (0/11) in the mesna group ($P = 0.00014$). This study, while smaller than that by Scheulen et al. [10], was randomized and controlled. However, the issue of blinding was not addressed.

Although each of the above two studies has its respective merits and defects, taken together, they provide level I evidence [8] in support of intravenous mesna use against standard prophylaxis for the prevention of ifosfamide-induced urotoxicity.

In a review of single-agent ifosfamide studies in sarcomas of soft tissue and bone, Benjamin et al. [9] summarized the uroprotective effects of NAC, and NAC compared with mesna. It appeared that NAC given with intravenous hydration was superior to either modality alone. However, this combination was still inadequate in patients receiving ifosfamide doses of 2 g/m^2 per day for 5 days, with grade 3 (>50 rbc/hpf or severe dysuria) and grade 4 (clots or unacceptable dysuria) toxicity seen in 25% of patients (14/56) in one trial. In a randomized study comparing NAC with mesna, ifosfamide 2 g/m^2 per day was administered for 5 days. The NAC dose was 1.5 g/m^2 every 4 h for three doses with each ifosfamide dose, and the mesna dose was 400 mg/m^2 per dose delivered according to the same schedule. None of the patients treated with mesna (0/31) developed grade 3 or 4 hematuria, whereas 16% of patients treated with NAC (5/31) developed grade 3 hematuria ($P = 0.04$). Hence, mesna was superior to NAC in preventing ifosfamide-induced urotoxicity.

Intravenous mesna dosing

Forty-eight clinical studies [12–59] using ifosfamide either alone or in combination with other chemotherapeutic agents in various tumor sites were reviewed. The total ifosfamide doses range from 2.02 g/m^2 to 17.5 g/m^2, and various administration schedules, such as continuous infusion over 24 h or short fractionated intravenous infusions given daily over several consecutive days, were used. In the majority of these studies mesna was administered at doses equal to 60–120% of the ifosfamide dose (Fig. 2).

The variability in the reporting of outcome among these 48 studies precludes accurate direct comparison of their urotoxicity data. While some of the studies provided details on treatment-related side effects, others focused mainly on efficacy and underreported toxicity.

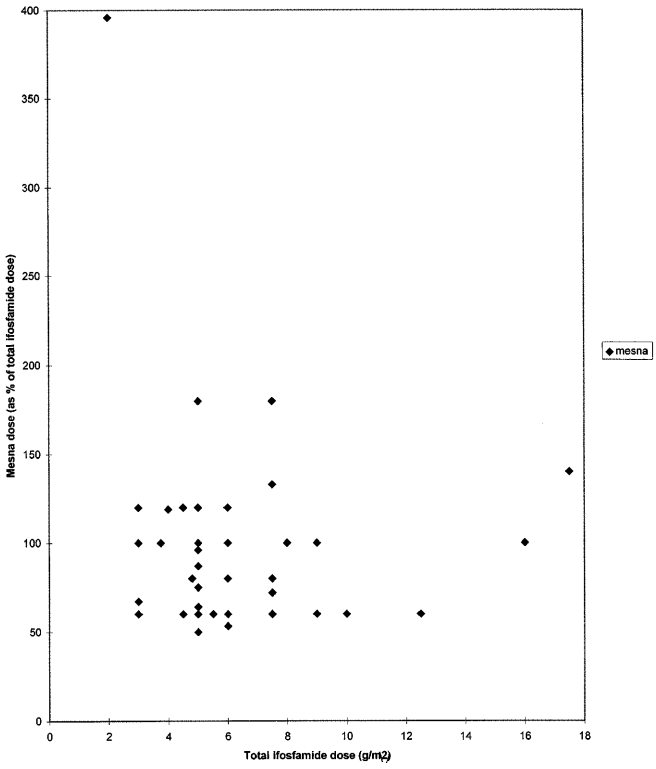

Fig. 2 Relationship between total ifosfamide dose and mesna dose. (Each ◆ represents a separate clinical study [12–59]

Furthermore, the classification of toxicities was not uniform, and different criteria were used by different authors. The frequency of toxicity was expressed as a percentage of the number of patients in some studies, and as a percentage of the number of chemotherapy cycles in others. Nevertheless, attempts were undertaken to detect any obvious correlation between the frequency of hemorrhagic cystitis (dysuria and/or macrohematuria) and either ifosfamide or mesna doses. Correlation analyses revealed no clear dose–effect relationship between these variables, regardless of whether the frequency of hemorrhagic cystitis was expressed as a percentage of patients or as a percentage of chemotherapy cycles delivered. Similarly, no significant correlation exists between ifosfamide dose or mesna dose and the frequency of microhematuria. The low incidence and severity of urotoxicity with mesna doses administered at 60% of a variety of ifosfamide doses suggest sufficient uroprotection with this mesna level. Mesna injected in three equal doses at 0 h, 4 h and 8 h after delivery of ifosfamide should be adequate to prevent dysuria or macrohematuria during a standard 3- or 5-day fractionated course of ifosfamide given in daily doses of 1–2 g/m^2. Fractionated ifosfamide therapy causes a rapid autoinduction of hepatic oxidative metabolism, and therefore leads to a time-dependent increase in the urinary excretion of its metabolites. Intravenous mesna given in the aforementioned empirical dosages and schedule has been shown to yield and maintain adequate urinary mesna concentrations throughout the course of therapy, despite the accelerated ifosfamide metabolism [64]. Since there are no direct comparisons of intravenous mesna doses in the literature, these observations provide inferential evidence for its dosing with ifosfamide.

Combined oral and intravenous mesna versus intravenous mesna

The best evidence comparing combined oral and intravenous mesna versus intravenous mesna alone comes from the study by Katz et al. [65]. In this study, 122 patients with various tumor types receiving any chemotherapy regimen with at least 3 consecutive days of ifosfamide were given three different schedules of mesna. In arm A, mesna was given at a dose equal to the ifosfamide dose, divided into three equal intravenous doses (33% of the ifosfamide dose each time), given 15 min before, and at 4 h and 8 h after ifosfamide infusion. In arm B, mesna was given at a dose equal to the ifosfamide dose, divided into three equivalent doses: intravenous 15 min before (33% of the ifosfamide dose), 4 h after (33% of the ifosfamide dose), and per os at 8 h after (66% of the ifosfamide dose) the ifosfamide treatment. In arm C, mesna was given at a dose equal to the ifosfamide dose and divided into two equal doses (50% of the ifosfamide dose each), both administered intravenously, 15 min before and 4 h after ifosfamide. A total of 225 cycles were evaluable. The incidences of severe hematuria (>50 rbc/hpf) were 0%, 0% and 3.03% in the three arms, respectively; this did not reach statistical significance when verified by Fisher's exact test. The results from this randomized study provide level I evidence that combined oral and intravenous mesna using the schedule as in arm B above is equivalent to intravenous mesna, at least when a total mesna dose equivalent to 100% of the ifosfamide dose is used.

Two other nonrandomized studies [36, 66] also used combined oral and intravenous mesna as uroprophylaxis against ifosfamide, and no macrohematuria, grade 3 or 4 hematuria, or hemorrhagic cystitis was reported from either. Bellmunt et al. [36] administered mesna at a dosage of 20% of the ifosfamide dose intravenously or 40% of the ifosfamide dose per os, at 1 h before and at 0 h, 4 h and 8 h after ifosfamide. The number of patients given oral mesna exclusively was not specified. Holoye et al. [66] administered intravenous mesna at 67.5% of the ifosfamide dose at 0 h, followed by fixed doses of oral mesna at 400 mg at 4 h and 8 h after ifosfamide. There were 23 episodes of grade 1 and 2 hema-

turia observed during a total of 148 cycles of chemotherapy.

In a recent comprehensive review of oral mesna administration with ifosfamide, Goren [67] summarized dosing schedules and the incidence of hematuria in 47 clinical studies. In this review, oral mesna was given to at least 1,986 patients, who received more than 6,475 courses of ifosfamide. Clinical data from the studies reviewed suggest that an initial intravenous dose of mesna (equal to 20% of the ifosfamide dose) followed by two oral doses (each equal to 40% of the ifosfamide dose) provides adequate uroprotection for daily doses of ifosfamide up to 2 g/m^2. Even among patients who received more intensive ifosfamide therapy, such as up to 5 g/m^2, the lowest doses of mesna studied (96%–128% of the ifosfamide dose) effectively limited hematuria. Despite these data, the most optimal schedule and dosage of combined oral and intravenous mesna administration have not been established.

Oral mesna versus standard prophylaxis

In one study by Araujo et al. [68], 70 patients with inoperable lung cancer were randomized, in a ratio of 2 to 1, to receive either mesna or standard prophylaxis. Oral mesna at 111% of the ifosfamide dose, was given in three equally divided doses at 0 h, 4 h and 8 h after ifosfamide infusion. Standard prophylaxis consisted of raised fluid intake and forced diuresis, with no specific details provided by the authors. All patients received intravenous ifosfamide at a dose of 2.25 g/m^2 daily for 4 consecutive days. Cystitis occurred in 76% of chemotherapy cycles (38/50) in the standard prophylaxis arm, versus 4.5% of chemotherapy cycles (4/88) in the mesna arm ($P < 10\text{-}17$). Gross hematuria was observed in 52% of chemotherapy cycles (26/50) in the standard prophylaxis arm, versus 0% of chemotherapy cycles (0/88) in the mesna arm ($P < 10\text{-}12$). This study provides level I evidence of the superiority of oral mesna over standard prophylaxis in the prevention of ifosfamide-induced urotoxicity.

Mesna use with cyclophosphamide

The efficacy of mesna for prevention of hemorrhagic cystitis after high-dose cyclophosphamide therapy has recently been reviewed [69]. Its superiority over intravenous hydration and/or bladder irrigation has not been proven conclusively. One small controlled trial [70] demonstrated that mesna plus 3 l/day of intravenous hydration was more effective than hyperhydration alone using 6 l/day of intravenous fluid. However, two larger randomized trials found no difference in efficacy between mesna therapy plus 1.5 l/m^2/day of intravenous hydration and hyperdration using 3 l/m^2 per day [71], or between mesna plus hyperhydration using 6 l/day and bladder irrigation plus hyperhydration using 6 l/day [72]. No study has evaluated whether mesna plus hyperhydration is superior to an equivalent hyperhydration regimen alone. The results of these studies are difficult to interpret because of confounding factors, such as the use of differing mesna and cyclophosphamide doses, variable methods of administration, and concomitant predisposing factors of hemorrhagic cystitis.

Toxicities of mesna

In general, adverse effects are uncommon with mesna, although oral administration may be associated with gastrointestinal effects such as nausea, vomiting and crampy abdominal pain. Nausea and vomiting are most probably secondary to the unpleasant taste of oral mesna solution, which can be partially masked by administering the drug with juice or carbonated beverages. Mesna tablets are more tolerable in flavor, but are so far only available in Europe.

Adverse effects are generally even less with intravenous doses of mesna, especially at the doses usually administered. There have been reports of diarrhea, abdominal pain, headache, limb and joint pain, transient lowering of blood pressure and increases in heart rate. These reactions occurred at doses of 60 mg/kg or more, given as a single bolus. Allergic reactions consisting mainly of itching and urticaria have been reported only rarely following intravenous administration of mesna, and these effects respond to treatment with antihistamines and corticosteroids [1].

There is no evidence that co-administration of mesna interferes with the antitumor effect of ifosfamide, either in preclinical data or in clinical studies. In multiple experimental animal tumor models, the addition of mesna did not affect the therapeutic activity of oxazaphosphorines [73, 74]. In the clinical setting, the possible interaction of mesna with the antiproliferative action of ifosfamide can be assessed by studying ifosfamide-induced myelosuppression with and without mesna. Fukuoka et al. [60] demonstrated similar hematological toxicities from ifosfamide whether it was given with mesna or with placebo. Furthermore, no significant difference in tumor response was observed ($P = 0.7898$). In the study comparing oral mesna with conventional prophylactic measures, Araujo et al. [68] found no appreciable differences between the two treatment arms with respect to the ifosfamide-associated hematological toxicities.

At the Princess Margaret Hospital, each 10-ml ampule contains 1000 mg of mesna and cost CDN $43 in 1996. The unit cost is identical for oral and intravenous mesna, since mesna in the intravenous formulation can

be safely taken per os. Because of its reduced bioavailability, the oral mesna dose is prescribed as twice the intravenous dose, thus doubling its cost. However, the costs of intravenous administration, nursing time, hospitalization fee, etc. have to be considered. Oral dosing, if proven to be as efficacious as intravenous administration, may eliminate the need for patient hospitalization and therefore reduce overall cost.

Conclusions and recommendations

Although mesna prophylaxis has been extensively utilized to counteract ifosfamide-induced urotoxicity in a large number of malignancies, there have been few studies designed primarily to define its optimal formulation, dosage and scheduling. Many of the existent trials have methodological flaws, such as small sample sizes and poorly described outcome criteria. Variability in the pattern and focus of outcome reporting among published trials impedes meaningful direct correlation between the incidence of urotoxicty and either ifosfamide or mesna doses. Despite the paucity of well conducted studies, the cumulative weight of evidence in the literature firmly supports the concomitant use of mesna with ifosfamide administration. The following specific recommendations are evidence-based summaries to guide mesna delivery.

1. There is good evidence that mesna reduces ifosfamide-induced urotoxicity in the treatment of multiple tumor sites, and should be used concomitantly with any dosage of ifosfamide administration (grade A recommendation).

2. There is good evidence that intravenous mesna use is superior in its uroprotection to placebo, and to standard prophylaxis with vigorous hydration and alkalinization of urine. The incidences of relevant clinical outcomes, including subjective patient symptoms of dysuria and frequency, as well as macrohematuria, are reduced with intravenous mesna (grade A recommendation). A commonly used schedule that offers sufficient uroprotection involves the administration of mesna at doses equal to 60% of the ifosfamide dose, given in three divided doses, concurrent with or at 15 min before and then at 4 h and 8 h after ifosfamide. This schedule may be used with fractionated intermittent short-time intravenous infusions of ifosfamide given over several days.

3. There is good evidence that combined oral and intravenous mesna administered in some tested schedules is equivalent to intravenous mesna alone (grade A recommendation). One such schedule involves the administration of intravenous mesna 15 min before (33% of the ifosfamide dose) and 4 h after (33% of the ifosfamide dose), and per os at 8 h after (66% of the ifosfamide dose) the ifosfamide treatment. Other combined schedules have not been tested directly against intravenous mesna for their efficacy.

4. There is good evidence that oral mesna, given in a monitored setting to ensure compliance, is superior to standard prophylaxis against ifosfamide-induced urotoxicity (grade A recommendation). One tested schedule with proven efficacy involves the administration of oral mesna at 111% of the ifosfamide dose, given in three divided doses, at 0 h, 4 h and 8 h after ifosfamide.

5. There is fair indirect but no direct evidence that oral mesna alone is equivalent in effect to intravenous mesna or combined formulation use (grade C recommendation). With oral mesna use, the incidence of hemorrhagic cystitis appears to be less than 5%, which is comparable to the incidence in studies with intravenous or combined modality mesna.

Research agenda

Preclinical and clinical studies have confirmed the efficacy of mesna in the prevention of ifosfamide-induced urotoxicity. Abundant data already exist on the use of intravenous mesna, and additional studies seeking the lowest possible intravenous dose may therefore not be feasible or ethical, considering its proven benefit and minimal toxicity. Further research on the use of mesna should focus on the scheduling and pharmacology of its oral administration or combined intravenous and oral dosing. For example, there should be an effectiveness study comparing oral mesna use in the outpatient setting against other proven methods of administration in the hospital setting. The regimen suggested by Goren [67] consisting of an initial intravenous dose of mesna (equal to 20% of the ifosfamide dose) followed by two oral doses (each equal to 40% of the ifosfamide dose), can easily be delivered in the outpatient clinic. The issue of patient compliance with oral mesna needs to be addressed, especially if nausea and vomiting are associated with ifosfamide or other co-administered chemotherapeutic agents. Oral mesna in tablet form may be preferable to liquid mesna because of its more tolerable taste, and may thus improve patient compliance. Other modes of mesna delivery, such as by continuous subcutaneous administration [76], also appear promising. It is important to correlate pharmacological evaluations of the various mesna preparations with their clinical profile. If these alternative routes of mesna administration are shown to produce equivalent or better results than intravenous mesna, then pharmacoeconomic and cost utility analyses are logical future avenues to explore.

Uniformity in the reporting of clinical end-points needs to be established. Investigators can facilitate the assessment of mesna regimens by defining toxicities according to standardized criteria from the World Health

Organization or the National Cancer Institute, and by specifying both the number of patients and the number of chemotherapy cycles affected by urotoxicity. Risk factors that may predispose to ifosfamide-induced uroepithelial damage despite mesna prophylaxis need to be identified. Finally, longer term follow-up data of patients vis-à-vis late urotoxicity are lacking and should be collected. Ongoing exploration and research into the proper use of mesna will promote the uroprotective value of this drug in the clinical setting.

Acknowledgements The authors would like to thank Dr. E. Wang for her valuable comments and suggestions.

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