CLINICAL STUDIES[5)-7)]

The results of clinical studies conducted at 49 institutions in Japan are summarized as follows:

The response rate in 2,680 assessable cases was 39.1% (1,049/2,680). (Cases which were judged to be 1-A or better by Karnofsky criteria or classified as “remission” by the criteria of the Japan Society for Cancer Therapy or equivalent cases were evaluated as responded.)

(Data for drug reevaluation, 1982)

The response rate in the patients treated with Mitomycin C alone was 39.4% (488/1,239), and response rates by the type of cancer were as indicated in the below table.

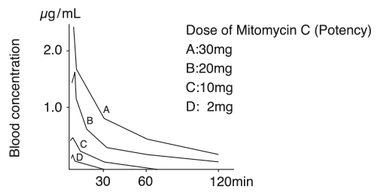
Disease	Response rate (responded/treated)	
Gastric cancer	29.7%	(131/441)
Colorectal cancer	34.4%	(11/32)
Lung cancer	36.7%	(87/237)
Liver cancer	29.4%	(5/17)
Uterine cancer	67.2%	(90/134)
Breast cancer	50.0%	(18/36)
Head and neck tumor	40.0%	(8/20)
Bladder tumor	76.9%	(40/52)
Chronic leukemia	95.0%	(19/20)

The response rate in the patients treated with Mitomycin C combined with any other therapy was 38.9% (561/1,441). Response rates by injection route were 35.8% (867/2,419) with intravenous injection, 66.5% (129/194) with intraarterial injection and 79.1% (53/67) with local infusion such as intravesical instillation.

5.2 Pharmacokinetic properties

5.2.1 Blood concentrations[1)]

Changes of blood concentrations of Mitomycin C after one shot of intravenous injection of 2 to 30mg / body in cancer patients are as follows:



Pharmacokinetic parameters[1)]

Parameter / Dosage	Half-life (min)		$AUC_{0\sim\infty}$ (μg/mL·min)
	$T_{1/2}\alpha$	$T_{1/2}\beta$	
10mg/body	1.3	32.9	10.0
20mg/body	4.7	41.2	42.8
30mg/body	5.2	50.2	98.9

(Reference: Data from US study)[2)]

Parameter / Dosage	n	CL (mL/min/m²)	V_1 (L/m²)	V_2 (L/m²)
6 to 8	9	314.7	9.0	23.0
10	9	320.8	9.6	32.2
15 to 20	12	355.6	10.1	23.6

5.2.2 Distribution

● **Distribution in tissues** (data from experiment with mice)[1)]

The concentration of Mitomycin C detected 5 minutes after intravenous administration of 8mg/kg of Mitomycin C in cancer model of mice was highest in the lung followed by skin, kidney, muscle, heart, small intestine, spleen, tumor, stomach and then by liver.

● **Protein binding rate** (by equilibrium dialysis)

Concentration (μg/mL)	0.1	1.0	10.0
Binding rate (%)	12.8	9.4	8.4

5.2.3 Metabolism (data from US *in vitro* study)[3)]

Mitomycin C is presumably metabolized to a reductant mainly in the liver and kidney, which is then activated or inactivated.

5.2.4 Excretion[4)]

The rate of recovery of unchanged Mitomycin C from urine within 4 hours after one shot injection of 10 to 30 mg/body of Mitomycin C in cancer patients was 4.3% to 8.8% of the dose.

5.3 Preclinical safety data

5.3.1 Carcinogenesis and mutagenesis

Mitomycin C has the potential for mutagenicity *in vitro* and *in vivo*.

Carcinogenicity has been reported in animal experiments with mice by subcutaneous administration and with rats by intraperitoneal or intravenous administration.

Animal studies with mice have shown teratogenicity of this drug manifested as developmental inhibition, cleft palate, hypoplastic tail, hypoplastic jaws, ectrodactyly, etc.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

6.2 Incompatibilities

Since the potency of Mitomycin C may be reduced when a low pH solution is used for reconstitution, it is recommended to use the solution soon after reconstitution. In addition it is recommended to avoid mixture with other low pH injectable solution.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

MITOMYCIN C 2 MG (potency)/vial: Package containing 10 vials

MITOMYCIN C 10 MG (potency)/vial: Package of 5 boxes containing 1 vial each

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORIZATION HOLDER

Dexcel Ltd

1 Dexcel street, Or-Akiva, 3060000, Israel

Manufactured and Distributed by:

Kyowa Hakko Kirin Co., Ltd.

1-6-1 Ohtemachi, Chiyoda-ku, Tokyo, Japan

The format of this leaflet was determined by the Israeli Ministry of Health (MOH) and its content was checked and approved by the Israeli MOH in: 05/2015

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MIT-S(2)(10) イスラエル

-ANTINEOPLASTIC AGENT-

Mitomycin-C Kyowa

MITOMYCIN C for Injection

1. NAME OF THE MEDICINAL PRODUCT

MITOMYCIN C 2 MG

MITOMYCIN C 10 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of MITOMYCIN C contains Mitomycin C 2 mg or 10 mg

For the full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Injectable solution to be reconstituted before use

Blue-purple crystalline powder

Brand name	MITOMYCIN C 2mg (2 mg potency/vial)	MITOMYCIN C 10mg (10 mg potency/vial)
pH range	5.5 to 8.5	5.5 to 8.5
Osmotic pressure ratio	Approx. 1 when reconstituted with 5ml of distilled water for injection (JP)	Approx. 1 when reconstituted with 25ml of distilled water for injection (JP)
Concentration of sodium chloride	0.96% when reconstituted with 5ml of distilled water for injection (JP)	0.96% when reconstituted with 25ml of distilled water for injection (JP)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remission of subjective and objective symptoms associated with the following diseases:

Chronic lymphocytic leukemia, chronic myelocytic leukemia, gastric cancer, colorectal cancer, lung cancer, pancreatic cancer, liver cancer, cervix cancer, cancer of endometrium, breast cancer, head and neck tumor and bladder tumor.

4.2 Posology and method of administration

1) Intermittent administration

Usually for adults, 4 to 6mg (potency)/day of Mitomycin C is administered intravenously once or twice a week.

2) Administration on consecutive days

Usually for adults, 2mg (potency)/day of Mitomycin C is administered intravenously every day.

3) Intermittent massive administration

Usually for adults, 10 to 30mg (potency)/day of Mitomycin C is administered intravenously every 1 to 3 weeks or at longer intervals.

4) Concurrent use with other antineoplastic agents

Usually for adults, 2 to 4mg (potency)/day of Mitomycin C is administered once or twice a week in combination with other antineoplastic agents.

Mitomycin C may be administered, if necessary, intraarterially, intrathecally, intrapleurally or intraperitoneally at a usual dose of 2 to 10mg (potency)/day of Mitomycin C in adults. The dosage may be adjusted depending on the age and symptoms of the patient.

(Preparation)

Reconstitute MITOMYCIN C Injection with 5ml of distilled water for injection (JP) per 2mg (potency) of Mitomycin C.

5) Use in patients with bladder tumor

For prophylactic use against recurrence, 4 to 10mg (potency) of Mitomycin C is usually administered intravesically once every day or every other day.

For therapeutic use, 10 to 40mg (potency)/day of Mitomycin C is administered intravesically once a day. The dosage may be adjusted depending on the age and symptoms of the patient.

4.3 Contraindications

Patients with a history of serious hypersensitivity or idiosyncratic reaction to any of the components of the product.

Thrombocytopenia, coagulation disorders and increased bleeding tendency.

4.4 Special warnings and precautions for use

Mitomycin C should be administered under the supervision of a physician experienced in cytotoxic cancer chemotherapy. Local ulceration and cellulitis may be caused by tissue extravasation during intravenous injection and utmost care should be taken in administration.

If extravasation occurs, it is recommended that the area is immediately infiltrated with sodium bicarbonate 8.4% solution, followed by an injection of 4 mg dexamethasone. A systemic injection of 200 mg of vitamin B6 may be of some value in promoting the regrowth of tissues that have been damaged.

Mitomycin C should not be allowed to come into contact with the skin. If it does, it should be washed several times with 8.4% sodium bicarbonate solution, followed by soap and water. Hand creams and emollients should not be used as they may assist the penetration of the drug into the epidermal tissue.

In the event of contact with eye, it should be rinsed several times with 8.4 % sodium bicarbonate solution. It should then be observed for several days for evidence of corneal damage. If necessary, appropriate treatment should be instituted.

4.4.1 Careful Administration (Mitomycin C should be administered with care in the following patients.)

1) Patients with hepatic or renal dysfunction
[Adverse reactions may be enhanced.]
2) Patients with bone marrow depression and bleeding tendency as these may be exacerbated
3) Patients complicated with infection
[Administration of this product may aggravate infection due to bone marrow depression.]
4) Patients with varicella
[Fatal systemic disorders may occur.]

4.4.2 Important Precautions

1) Patients should be carefully monitored with frequent laboratory testing (hematological test, liver function test, renal function test, etc.) because serious adverse reactions such as bone marrow depression may occur. If any abnormality is observed, appropriate measures such as reduction of the dose and suspension of administration should be taken. Additionally, Mitomycin C should be administered with care because long-term use of the product may cause enhanced adverse reactions, which may be protracted.
2) Severe renal toxicity has occasionally been reported after treatment and renal function should be monitored before starting treatment and again after each course.
3) Special cautions are required to the possible manifestation or aggravation of infectious disease and bleeding tendency.
4) Precautions should be paid to possible occurrence of acute leukemia (In some cases following preleukaemic phase) or myelodysplastic syndrome (MDS) in patients treated with Mitomycin C in combination with other antineoplastic agents.
5) Mitomycin C Injection should be administered with care in children, paying special attention to the manifestation of adverse reactions.
6) In case administration of this drug is required in children or patients with reproductive possibility, potential effects on gonad should be considered.

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品名	MIT-S イスラエル EF	本コード		作業者印	MC	AC	色調	スミ	トラップ	角度
制作日	2015.8.24 校 六校	仮コード	0330P0616203	津田			朝日印刷株式会社	mxjs8	APP.TB	

4.4.3 Precautions during administration

1) Since intravenous administration may cause vascular pain, phlebitis, thrombus, injection site induration, necrosis, Mitomycin C should be injected as slowly as possible, paying careful attention to the site and method of administration.
2) Since extravascular leakage of the drug solution may cause induration or necrosis at the injection site, this drug should be injected cautiously to avoid extravascular leakage of the drug solution.
3) Intraarterial administration may cause skin disorders such as ulcer, induration pain, redness, erythema, blisters and erosion in the region involved, which may lead to skin/muscle necrosis. Administration should be discontinued and appropriate measures should be taken, if any of such symptoms develops. In particular, parenchymatous liver disorder, biloma, cholangitis (also sclerosing), and bile duct necrosis may occur after hepatic arterial administration of the drug.
4) Since the influx of the drug solution into other sites than the targeted site in the administration to the hepatic artery may cause gastroduodenal ulcer, haemorrhage, perforation, etc., the location of the end of catheter and drug distribution area should be confirmed photographically or by other means, paying attention to possible deviation or shift of the catheter and infusion rate. Administration should be discontinued and appropriate measures should be taken, if any of such symptoms develops.
5) Since calcinosis, contracted bladder and cystitis associated with dysuria and pollakiuria, bladder perforation, bladder necrosis, penile necrosis may occur in patients receiving intravesical Mitomycin C injection, the drug should be carefully injected.

4.4.4 Pediatric Use

The safety of Mitomycin C in small for dates babies, neonates, infants and children has not been established. [See **4.4.2 Important Precautions** 4) and 5).]

4.4.5 Use in the Elderly

Because elderly patients often have reduced physiological function, bone marrow depression, which may be protracted, and renal disorder are likely to occur; Mitomycin C should be administered cautiously in elderly patients while closely monitoring patient's condition and paying special attention to the dose and dosing interval.

4.4.6 Precaution for preparation

Since the potency of Mitomycin C may be reduced when a low pH solution is used for reconstitution, it is recommended to use the solution soon after reconstitution. In addition it is recommended to avoid mixture with other low pH injectable solution.

4.4.7 Other Precautions

Genesis of various types of tumors has been reported in animal experiments with mice by subcutaneous administration and with rats by intraperitoneal or intravenous administration.

4.5 Interaction with other medicinal products and other forms of interaction

Precautions for Coadministration

[Mitomycin C should be administered with care when coadministered with the following drugs.]

Drugs	Signs, Symptom and Treatment	Mechanism and Risk Factors
Other antineoplastic agents Irradiation	Adverse reactions such as bone marrow depression may be enhanced.	Adverse reactions of each other drugs are enhanced.
Vinca alkaloid antineoplastic agents Vincristine sulfate Vinblastine sulfate Vindesine sulfate etc.	Breath shortness and bronchospasm may occur.	Mechanism of action is not known.

4.6 Pregnancy and lactation

Pregnancy:

Administration of Mitomycin C is not recommended in pregnant women or women who may possibly be pregnant.

[Animal studies with mice have shown teratogenicity of this drug manifested as developmental inhibition, cleft palate, hypoplastic tail, hypoplastic jaws, ectrodactyly, etc.]

Breast-feeding:

Nursing mothers should discontinue breast feeding during treatment.[The safety of Mitomycin C in nursing mothers has not been established.]

4.7 Effects on ability to drive and use machines

Generalised weakness and lethargy have been reported on rare occasions. If affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

(At the end of reevaluation)

The main adverse reactions collected from literature at the time of reevaluation were leucopenia in 130 (40.2%) of 323 patients, thrombocytopenia in 75 (24.7%) of 304 patients, anorexia in 58 (21.8%) of 266 patients, nausea/vomiting in 41 (15.4%) of 266 patients, malaise in 15 (5.6%) of 266 patients, weight loss in 18 (5.5%) of 329 patients, bleeding tendency in 12 (3.6%) of 329 patients and anaemia in 10 (3.0%) of 329 patients.

Patients should be monitored closely during each course of treatment, paying particular attention to peripheral blood count including platelet count. No repeat dose should be given unless the leukocyte count is above 3.0×10^9/L or more and the platelet count is 90×10^9/L or more. The nadir is usually around four weeks after treatment and toxicity is usually cumulative, with increasing risk after each course of treatment. If disease progression continues after two courses of treatment, the drug should be stopped since the chances of response are minimal.

Clinically significant adverse reactions

- Marrow depression such as pancytopenia, leucopenia, neutropenia, thrombocytopenia, haemorrhage and anaemia may occur. Patients should be carefully observed with periodical testing, and, if any signs of abnormality are noted, appropriate measures such as reducing the dose and suspending administration should be taken.
- Haemolytic-uraemic syndrome and microangiopathic haemolytic anaemia may occur. Patients should be carefully observed with periodical testing, and, if symptoms such as anaemia with fragmented red blood cells, thrombocytopenia and renal dysfunction are observed, appropriate measures such as discontinuing treatment should be taken.
- Nausea and vomiting are sometimes experienced immediately after treatment, but these are usually mild and of short duration.
- *Renal and urinary disorders:*
  Serious renal disorder such as acute renal failure may occur. Patients should be carefully observed, and, if any abnormal change is noted in BUN, creatinine, creatinine clearance, etc., appropriate measures such as discontinuing treatment should be taken.
- *Immune system disorders:*
  Shock or anaphylactoid reaction may occur, patients should be carefully observed. If symptoms such as itching, rash, flushing, sweating, dyspnoea and decreased blood pressure occur, treatment should be immediately discontinued and appropriate measures should be taken.
- *Respiratory, thoracic and mediastinal disorders:*
  Pulmonary toxicities such as pulmonary oedema, interstitial pneumonia, pulmonary fibrosis (accompanied by fever, coughing, dyspnoea, abnormal findings on chest X-ray and eosinophilia), etc. may occur. Treatment should be discontinued and appropriate measures such as administration of adrenal cortex hormone should be taken, if any of these signs is observed.
- *Hepatobiliary disorders*
  Administration to the hepatic artery may cause liver and biliary tract disorders (cholecystitis, cholangitis (also sclerosing), biloma, bile duct necrosis, parenchymatous liver disorder, etc.). Drug distribution area should be confirmed photographically or by other means, and treatment should be discontinued and appropriate measures should be taken if any of abnormal signs is noted.
- *Skin disorders*
  Skin toxicity may occur in a small proportion of patients, with side effects such as alopecia (although this is less frequent and less severe than with certain other cytotoxic agents). Bleeding, rashes and mouth ulcers have been reported.
  The following administration related adverse reactions have also been reported: muscular pain, phlebitis, thrombus, induration or necrosis at the injection site, pain, redness erythema, blisters, erosion and ulceration which may lead to skin/muscle necrosis.

Other adverse reactions

Such adverse reactions as listed in the below table may occur. Patients should be carefully observed, and, if any abnormality occurs, appropriate measures such as reducing the dose and suspending administration should be taken.

MedDRA (Medical Dictionary of Regulatory Activities) terminology was used to describe system/organ classes and adverse events (represented by Low Level Terms). The adverse drug reactions are presented by system/organ class, and are ranked by frequency, using the follow convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	cannot be estimated from the available data

Infections and infestations	
Not known	Infection bacterial, viral or fungal infections, sepsis and septic shock
Neoplasms benign, malignant and unspecified	
Not known	Myelodysplastic syndrome, acute myeloid leukemia and acute leukemia
Blood and lymphatic system disorders	
Not known	Bone marrow suppression with thrombocytopenia and leucopenia, anemia and hemorrhage, granulocytopenia, febrile neutropenia, erythropenia, thrombotic thrombocytopenic purpura
Immune system disorders	
Not known	Hypersensitivity, anaphylactoid reaction, anaphylactic shock (eosinophilia, sweating, decreased blood pressure, dyspnoea)
Metabolism and nutrition disorders	
Very common	Anorexia
Not known	Weight loss
Vascular disorders	
Not known	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Not known	Respiratory disorders such as Interstitial lung disease, pulmonary fibrosis, bronchospasm, pneumonitis and coughing
Gastrointestinal disorders	
Very common	Nausea and vomiting
Not known	Stomatitis, diarrhoea, constipation, abdominal discomfort
Hepatobiliary disorders	
Not known	Parenchymatous liver disorder, cholecystitis, jaundice, hepatic damage
Skin and subcutaneous tissue disorders	
Not known	Rash, erythema, pruritis, alopecia
Renal and urinary disorder	
Very common	Cystitis, haematuria
Not known	Atrophy of bladder, acute renal failure, renal disorder, proteinuria, albuminuria, contract bladder (pollakiuria, disuria), calcinosis, bladder necrosis, bladder perforation, penile necrosis
General disorders and administration site conditions	
Very common	Malaise
Not known	Pyrexia (chills), oedema, injection site phlebitis, induration associated with extravasation, necrosis associated with extravasation, generalized weakness and lethargy

4.9 Overdose

Some cases of overdose have been reported to the manufacturer. An increase in the more common side effects should be expected, such as fever, nausea, vomiting and myelosupression. Strict monitoring of the patient and appropriate treatment should be perfomed.

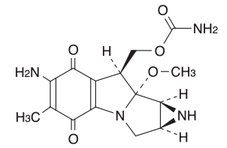
5. PHARMACOLOGICAL PROPERTIES

Nonproprietary name : Mitomycin C

Chemical name : (1a*S*, 8*S*, 8a*R*, 8b*S*)-6-Amino-4,7-dioxo-8a-methoxy-5-methyl-1-1,1a,2,8,8a,8b-hexahydroazirino[2′,3′ : 3,4]pyrrolo[1,2-*a*]indol-8-ylmethyl carbamate

Molecular formula : $C_{15}H_{18}N_4O_5$=334.33

Structural formula :



Description : Mitomycin C occurs as a blue-purple crystal or crystalline powder.

Solubility : It is freely soluble in N, N-Dimethylacetamide, slightly soluble in water or methanol, very slightly soluble in ethanol (99.5) and practically insoluble in ether.

Stability : Mitomycin C in crystalline state is stable at temperature of 15-25 degree Celsius. In the state of solution, it is susceptible to pH alteration; it is stable at pH 8.0 but it becomes less stable with reduction in pH value at 7.0 or lower pH.

Partition coefficient : logP′oct = – 0.53
[measured by flask-shaking method using *n*-octanol/pH 7.4 buffer solution]

5.1 Pharmacodynamic properties

5.1.1 Mechanism of Action[10)-11)]

Mitomycin C is presumed to exert its antineoplastic activity by combining with DNA in tumor cells and inhibiting DNA replication through the formation of cross-linkage to double stranded DNA. It has been evidenced that cells in the latter G1 phase of DNA synthesis through the early S phase of DNA synthesis are highly sensitive to Mitomycin C.

5.1.2 Action/effects[8)-9)]

Mitomycin C administered intraperitoneally at a dose of 1 to 2mg/kg in mice and rats transplanted with various tumors demonstrated a potent antineoplastic activity against Ehrlich's carcinoma, Sarcoma 180, Leukemia P388, Yoshida's sarcoma, etc., suggesting a broad anticancer spectrum.

品名 MIT-S イスラエル EF 本コード 作業者印 MC AC 色調 スミ トラップ 角度
制作日 2015.8.24 校 六校 仮コード 0330P0616203 津田 朝日印刷株式会社 mxjs8 APP.TB