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Endoscopic submucosal dissection for rectal carcinoid tumors

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Abstract
Background Endoscopic submucosal dissection (ESD) has an advantage over endoscopic mucosa resection (EMR) by enabling removal of gastrointestinal neoplasms en bloc. The ESD procedure is the treatment of choice for rectal carcinoids that have classic histologic architecture with minimal cellular pleomorphism and sparse mitoses, but it has not been applied for such tumors.
Methods The ESD procedure was performed for patients with colorectal tumors that fulfilled the inclusion criteria specifying tumor with a diameter of 10 mm or less, no muscular layer invasion, and no metastases to the lymph nodes or distal organs. The ESD procedure was performed for patients with rectal carcinoids but no node or distal metastasis.
Results This study enrolled 20 rectal carcinoid tumors from 20 consecutive patients. The mean tumor size was 7.6 mm (range, 3–16 mm). En bloc removal was achieved for all the tumors, and the complete resection (en bloc with tumor-free lateral/basal margins) rate was 90% (18/20). The two cases in which the margins were not evaluable due to burn effects still are free of recurrence and metastasis at this writing. Perforation was seen in one case, which was managed nonsurgically.
Conclusions Precise histolopathogic assessment of the specimens resected en bloc by ESD may reduce tumor recurrence and metastasis after ESD. As the treatment of choice for small rectal carcinoids, ESD is associated with nominal risks of metastatic disease.

Keywords Carcinoid · Complete resection · En bloc resection · Endoscopic submucosal dissection · Rectum

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Rectal carcinoids are uncommon tumors, representing 1.8% of anorectal neoplasms [1]. We currently can diagnose small rectal carcinoid tumors at an early stage [2]. Rectal carcinoid tumors with a diameter of 10 mm or less and contained within the submucosal layer can be treated by local excision via endoscopy because they rarely metastasize [2, 3]. Complete resection of rectal carcinoid tumors is, however, difficult with conventional endoscopic resection because these tumors extend to the submosa [4].

Endoscopic submucosal dissection (ESD) was developed to dissect directly along the submucosal layer for

gastric epithelial neoplasia [5, 6]. The ESD procedure has an advantage over conventional endoscopic mucosal resection (EMR) by enabling en bloc removal of upper gastrointestinal tumors irrespective of their size [5, 6]. Several studies have shown encouraging results with the use of ESD for epithelial neoplasms in the colon and rectum [7–10]. Such colorectal lesions commonly have been treated with EMR in multiple segments [10], but ESD allows precise histologic assessment of the specimens excised in the one piece with tumor-free lateral/basal margins. Therefore, ESD may prevent residual disease and local recurrence [8, 10].

This study aimed to evaluate the efficacy and safety of ESD for the treatment of small rectal carcinoid tumors.

Patients and methods

Between February 2005 and April 2008, 20 rectal carcinoid tumors diagnosed by endoscopic biopsies for 20 consecutive patients were treated by ESD at the hospitals of Nagasaki University School of Medicine. The inclusion criteria specified a tumor 10 mm or less in diameter, no muscular layer invasion, and no metastases to lymph nodes or distal organs.

After standard coloproctoscopy and chromoendoscopy with 0.5% indigo carmine, endoscopic ultrasolography (EUS) was performed to evaluate the depth of tumor invasion and the involvement of pararectal lymph nodes. Based on the Japanese Classification of Colorectal Carcinoma [11], the location of tumors (Rb, Ra, and Rs) was classified in terms of borders 1 cm, 6 cm, 12 cm above dentate line (DL) as follows: Rb (1.1–6.0 cm above DL), Ra (6.1–12 cm above DL), and Rs (12.1–15 cm above DL). The existence of lymph node and distant metastasis was surveyed by contrast-enhanced computed tomography (CT) and ultrasound sonography of the abdomen and chest X-ray.

Under written informed consent, the ESD procedures, described previously in detail [12], were performed, with modifications for the tumors of the rectum. A solution of 10% glycerin plus 5% fructose in 0.9% saline was injected into the submucosal layer to the elective lesions. A mucosal incision was made circumferentially around the lesion using the FlushKnife (Fujinon-Toshiba ES System Co., Omiya, Japan) (Fig. 1B). Submucosal dissection was performed for complete removal of the lesion using the tip-typed knife (Fig. 1C, D). High-frequency generators (ICC200; ERBE Elektromedizin GmbH, Tübingen, Germany) were used in the Endo cut mode at Effect 3 (80 W) for incision of the mucosa, and in the forced coagulation mode at Effect 2 (40 W) for exfoliation of the submucosa.

To control bleeding during ESD or to prevent possible bleeding from visible vessels in the artificial ulcer immediately after the resection, a hemostatic forceps (Coagrasper, Olympus, Tokyo, Japan) was used in the soft coagulation mode (60 W). All the patients were sedated by intravenous injection of 5–7.5 mg of diazepam and 15 mg of pentazocine. For conscious sedation, 2.5 mg of diazepam was given additionally as needed throughout the procedure.

Procedure-related bleeding after ESD was defined as bleeding that required transfusion or surgical intervention or as bleeding that caused the hemoglobin level to fall by 2 g/dl [11]. Perforation was diagnosed endoscopically or by the presence of free air on an abdominal plain radiograph or by CT.

The excised specimens were fixed in 10% buffered formalin, embedded in paraffin, sectioned perpendicularly at 2-mm intervals, and stained with hematoxylin and eosin (Fig. 1E, F). Tumor size, depth of invasion, and histologic atypia including active mitosis, lymphatic, and vascular involvement were assessed, together with tumor invasion to the lateral and basal margins.

En bloc resection refers to a resection in one piece [13]. Resection was deemed complete when the tumor was removed en bloc with tumor-free lateral and basal margins (R0) [7, 8]. They were considered incomplete when tumors were excised in multiple segments or with lateral/basal margins positive for tumor invasion (R1), or when the margins were not evaluable due to artificial burn effects or insufficient reconstruction of the piecemeal fragments (Rx) [7, 8]. After histopathologic assessment, additional surgical intervention with removal of regional lymph nodes was recommended in the case of tumors with invasion into the muscularis propria, poorly differentiated or undifferentiated tumors, or vessel infiltration of tumor cells.

Endoscopic examinations were scheduled 3, 6, and 12 months after ESD and then annually. Biopsy specimens during each follow-up endoscopy were taken from the treatment-related scar or any other suspicious abnormalities for assessment to determine the presence of local recurrent tumor. To detect lymph node and distant metastasis, abdominal CT, ultrasound sonography, and chest X-ray were examined annually by each doctor in charge.

Results

The study findings for the enrolled 20 rectal carcinoids are summarized in Table 1. The mean age of the 20 patients (11 men and 9 women) was 60 years (range, 42–79 years). All but one patient, who reported rectal bleeding (case 7), were asymptomatic, and none had symptoms or signs of carcinoid syndrome. The mean diameter of the tumors was 7.6 mm (range, 3–6 mm; median, 7 mm). There were three cases (cases 2, 5, and 20) of rectal carcinoids larger than

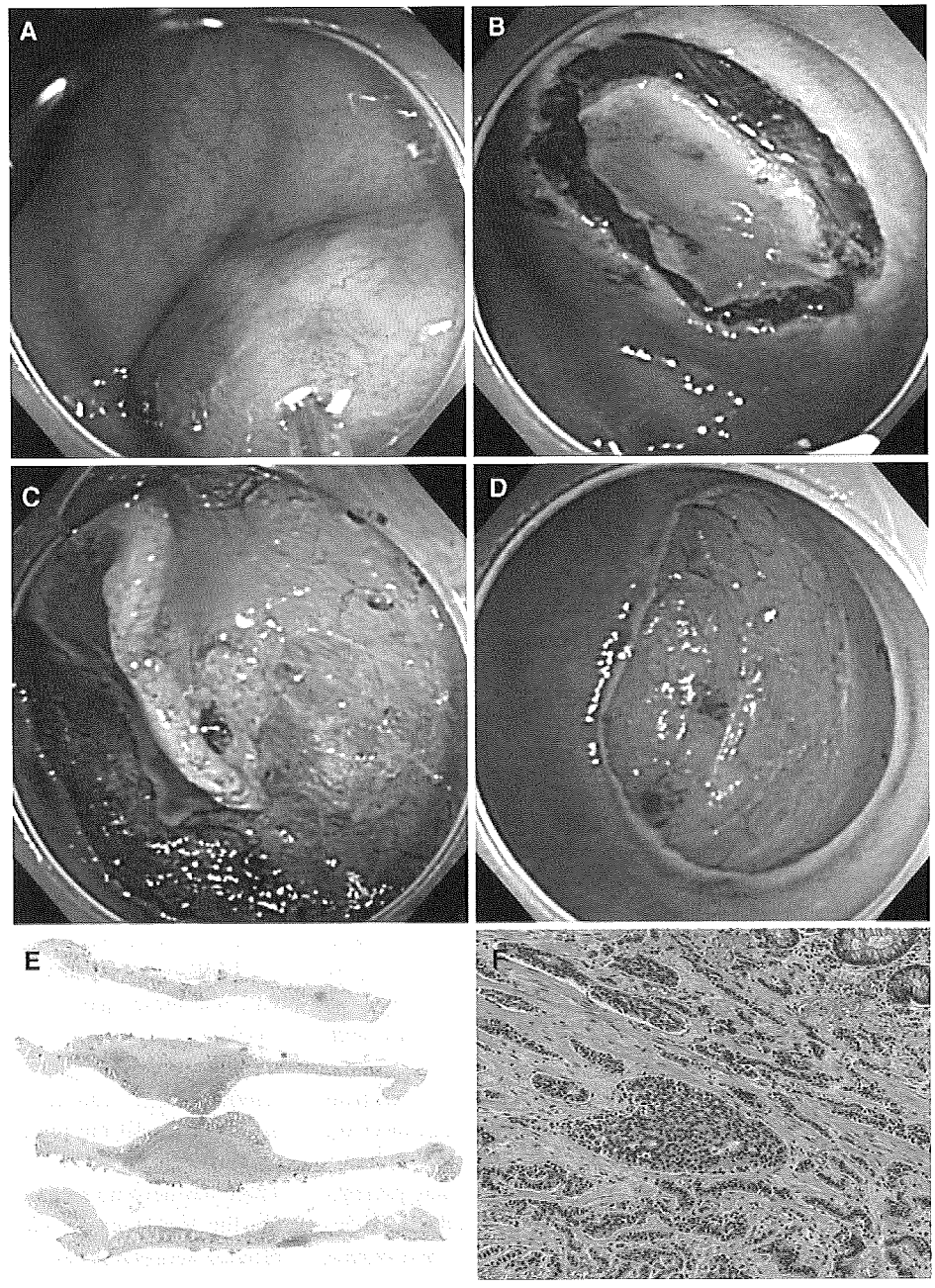

Fig. 1 **A** To lift the yellow-whitish submucosal nodule, a solution of 10% glycerin plus 5% fructose in 0.9% saline was injected into the submucosal layer. **B** A mucosal incision was made circumferentially around the lesion. **C** Submucosal dissection was performed. **D** Complete tumor removal was achieved. **E** Low-power photomicrograph shows a carcinoid tumor resected en bloc with tumor-free lateral/vertical margins (hematoxylin and eosin stain). **F** The tumor had classic histologic architecture of trabecular, insular, or ribbon-like cell clusters with minimal cellular pleomorphism and sparse mitoses (magnification ×100, hematoxylin and eosin stain)

10 mm, with surgical interventions refused. There were 17 rectal tumors located in the Rb and 3 located in the Ra.

With respect to macroscopic appearance, all but one tumor with a central depression showed solitary sessile polyp with a smooth surface. All the tumors were confined to the submucosa on EUS. None showed metastatic disease to lymph nodes or distal organs on preoperative examinations.

All the tumors were removed in an en bloc fashion. The median time for ESD treatment in the current series was 45 min (range, 20–140 min; mean, 54.5 min). Of the 20 lesions, 2 could not be evaluated for resectability due to difficulties in histopathologic assessment attributable to the burn effect. Complete resection was achieved for the remaining 18 lesions (90%, Table 1). Considering the nominal risk for metastatic disease, the two cases (cases 12 and 18), at this writing, have been under careful follow-up assessment 10 and 27 months since ESD.

All the carcinoid tumors were located in the submucosal layer and had classic histologic architecture of trabecular, insular, or ribbon-like cell clusters with minimal cellular pleomorphism and sparse mitoses (Fig. 1F). No lympho-vascular invasion was observed in any of the tumors. The

Table 1 Clinicopathologic characteristics of 20 rectal carcinoids treated by endoscopic submucosal dissection

Case no.	Age (years)	Sex	Central depression	Location[a]	Depth of invasion	Size (mm)	Resection	Vessel invasion	Perforation	Follow-up (mos)
1	75	F	Absent	Rb	Submucosa	5	R0	Absent	None	34
2	51	M	Present	Rb	Submucosa	12	R0	Absent	None	34
3	75	F	Absent	Ra	Mucosa	5	R0	Absent	None	33
4	42	M	Absent	Rb	Submucosa	7.5	R0	Absent	None	26
5	69	M	Absent	Rb	Submucosa	16	R0	Absent	None	23
6	50	M	Absent	Rb	Submucosa	8	R0	Absent	None	21
7	59	M	Absent	Rb	Submucosa	3	R0	Absent	None	12
8	61	F	Absent	Rb	Submucosa	5	R0	Absent	None	12
9	66	F	Absent	Rb	Submucosa	8	R0	Absent	Perforation	32
10	59	M	Absent	Rb	Submucosa	5	R0	Absent	None	29
11	64	F	Absent	Rb	Submucosa	10	R0	Absent	None	4
12	45	F	Absent	Rb	Submucosa	3	Rx	Absent	None	27
13	45	M	Absent	Rb	Submucosa	10	R0	Absent	None	12
14	56	F	Absent	Rb	Submucosa	4	R0	Absent	None	23
15	30	M	Absent	Rb	Submucosa	10	R0	Absent	None	9
16	61	F	Absent	Rb	Submucosa	7	R0	Absent	None	7
17	79	M	Absent	Ra	Submucosa	8	R0	Absent	None	12
18	65	M	Absent	Rb	Submucosa	6	Rx	Absent	None	10
19	72	M	Absent	Ra	Submucosa	5	R0	Absent	None	6
20	70	F	Absent	Rb	Submucosa	15	R0	Absent	None	21

R0 complete resection with tumor removed en bloc with tumor-free lateral and basal margins; *Rx* incomplete resection with margins not evaluable due to artificial burn effects or insufficient reconstruction of the piecemeal fragments

[a] Indication of Rb, Ra, and Rs was requested, with borders set up at 1 cm, 6 cm, and 12 cm above the dentate line (DL), as Rb (1.1–6.0 cm above DL), Ra (6.1–12 cm above DL), and Rs (12.1–15 cm above DL)

procedure-related bleeding, by definition, was not seen in any tumor. Perforation related to ESD was experienced by one patient (5%) but was successfully managed by conservative medical treatment after endoscopic closure with clipping.

One patient was lost to follow-up assessment for clinical outcomes of recurrence, metastatic disease, and survival. Neither local recurrence nor metastases to lymph nodes or distal organs was found in any of the 19 remaining patients during the mean follow-up period of 19.3 months (median, 21 months; range, 4–34 months). No patients died during the study period.

Discussion

Most rectal carcinoids extend into the submucosa, as shown in the current study, and neither conventional polypectomy nor EMR can remove the tumors completely. The rates for complete resection of rectal carcinoids with EMR range from 28.6 to 57.1% [14–16].

To improve resectability, various types of endoscopic resection techniques such as strip biopsy, EMR with cap aspiration, and endoscopic submucosal resection with a ligation device have been described as effective. Indeed, the EMR-based treatment results reached 82.9–100% [14–18], but these rates were based on a limited number of cases.

In the current study, we for the first time applied ESD to remove rectal carcinoids, and en bloc resection was achieved for all the tumors. Complete resection was comparably achieved for 90% (18/20) of the current series. There has been no local recurrence or metastasis since ESD for the two tumors with Rx resection. Thus, ESD can provide acceptable resectability for rectal carcinoid tumors by facilitating en bloc resection.

The majority of rectal carcinoids are small, with 86% of the tumors smaller than 10 mm in diameter [17]. Metastasis occurs in 5–15% of tumors measuring 10 to 19 mm, but the frequency increases to 80% for tumors 20 mm in size or larger [19]. Thus, rectal carcinoids that are 10 to 19 mm in size do not have predictable behavior, and there is no consensus in the literature concerning the appropriate therapy for tumors of this size, with some deciding for rectal resection and others recommending transanal excision for selected patients [4]. In the current study, the three tumors ranging from 10 to 19 mm in size were completely resected by ESD.

Besides tumor size, the risks of metastasis are related to the finding of a central depression, an infiltration into the muscularis propria, a vascular or lymphatic invasion, or a high proportion of mitotic cells at histologic examination [17, 18]. Because the atypical clinicopathologic features of carcinoids were not observed with any of the tumors in this study, the three aforementioned cases have been under careful follow-up assessment. They still were free of recurrence and metastasis at the last outpatient clinic visit.

The ESD procedure has the advantage over EMR by enabling removal of larger gastrointestinal lesions in an en bloc manner, irrespective of size [5, 6]. Because ESD allows precise histologic assessment of the resected specimen, this procedure is likely to be a treatment of choice for selected rectal carcinoids. These selected cases involve smoothly marginated tumors measuring 10 to 19 mm that still are confined to the submucosal layer and have no histologic atypia suggesting metastatic risks [17, 18].

The ESD procedure still poses a considerably high risk for perforation. The reported perforation rates for the colon and rectum were rather higher those for the stomach, varying from 1.4 to 10.4% [7, 8, 10]. Thus, the safety profiles associated with ESD have not been established for the colorectum.

In the current series, perforation occurred for an 8-mm tumor located in the Rb. Because the rectal wall of the Rb is thicker and supported by surrounding connective tissue [20], the case was successfully managed nonsurgically after endoscopic closure. However, surgical treatment after colorectal perforation is more risky than after gastric perforation due to peritonitis caused by fecal fluid leakage [10].

In its current stage of development, standardization of ESD for rectal carcinoids is premature [10]. The procedure should be applied as clinical research by experienced endoscopists.

In conclusion, ESD provided acceptable resectability for rectal carcinoids, most of which had a diameter of 10 mm or less. It is feasible to assess histologic atypia of the resected specimens precisely, thereby reducing recurrence and metastasis.

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Long-term trends of the incidence of hepatocellular carcinoma in the Nagasaki prefecture, Japan

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Abstract. The incidence of hepatocellular carcinoma (HCC) in Japan is still increasing. The aim of the present study was to analyze the epidemiological trend of HCC in the Western area of Japan, Nagasaki. A total of 1,807 patients with HCC diagnosed at our two hospitals between 1981 and 2005 were consecutively recruited for this study. Cohorts of patients with HCC were categorized into five-year intervals. The etiology of HCC was categorized into four groups: HCC-B: HBsAg positive, HCVAb negative, HCC-C: HCVAb positive, HBsAg negative, HCC-BC: both of HBsAg and HCVAb positive and HCC-nonBC: both of HBsAg and HCVAb negative. The number and proportion of HCC-B cases decreased from 1986 to 1990 and thereafter stabilized, whereas those of HCC-C reached the peak from 1995 to 2000 and thereafter decreased. On the other hand, the number and ratio of the HCC-nonBC cases continued to increase in the whole period. The male/female ratio of HCC-C patients decreased from 6.4 in the period 1981-1985 to 1.9 in 2001-2005, indicating clearly the increase of female patients. On the other hand, the male/female ratio of other types of HCC patients did not change during the period. HCC patients rapidly increased from 1981 to 2000 and this increase was originated from that of HCC-C. The increase of the median age and the number of female patients with HCC-C was also demonstrated. The increase in the number and the proportion of the HCC-nonBC patients was also significant.

Introduction

Primary liver cancer is the most common primary cancer of the liver accounting for ~6% of all human cancers. It is estimated that half a million cases occur worldwide annually, making primary liver cancer the fifth most common malignancy in men and the ninth in women (1-6). Hepatocellular carcinoma (HCC) accounts for 85 to 90% of primary liver cancers (7) and the age-adjusted HCC mortality rate has increased in recent decades in Japan (8). Similarly, a trend of increasing rates of HCC has been reported from several developed countries in North America, Europe and Asia (9,10). HCC often develops in patients with liver cirrhosis caused by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, or nonalcoholic fatty liver disease. Of the hepatitis viruses which cause HCC, HCV is predominant in Japan (11-14).

Although the age-adjusted incidence of HCC has increased in Japan, sequential changes in background features of HCC patients are not fully understood (15). Yoshizawa reports that deaths due to HCC in Japan have continued to increase in males, particularly in those older than 60 years of age in the past 3 decades, although the reasons for this are unclear (16). To clarify factors affecting epidemiological changes in Japanese HCC patients, especially the change in age distribution and gender, we analyzed the underlying features of HCC patients in a two major liver center-based study.

Patients and methods

Patients. A total of 1,807 patients with HCC diagnosed between January 1981 and December 2005 in the Liver Disease Center, National Nagasaki Medical Center and in the outpatient clinic of The First Department of Internal Medicine, Nagasaki University Hospital, were consecutively recruited for this study. The diagnosis of HCC was based on AFP levels and imaging techniques including ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI), hepatic angiography (HAG) and/or tumor biopsy. The diagnostic criteria for HCC were either a confirmative tumor biopsy or elevated AFP (≥20 ng/ml) and neovascularization in HAG and/or CT. Cohorts of patients with HCC were categorized into five-year intervals (1981-1985, 1986-1990, 1991-1995, 1996-2000 and 2001-2005).

Etiology of HCC. Sera were stored at -80°C until use. A diagnosis of chronic HCV infection was based on the presence of HCVAb (microparticle enzyme immunoassay; Abbott

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Key words: hepatitis C virus, hepatocellular carcinoma, aging, Japan

Table I. The characteristics of HCC patients, 1981-2005.

Period	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	Total
Number	240	316	369	419	463	1807
Gender						
Male	194	257	268	314	314	1347
Female	46	59	101	105	149	460
Ratio (male/female)	4.2	4.4	2.7	3.0	2.1	2.9
Age (y.o) (IQR)	57 (6.5)	61 (5.1)	63 (5.4)	66 (5.1)	68 (6.3)	64 (6.5)
Hepatitis virus						
HCC-B	95	70	80	67	100	412
HCC-C	111	213	240	292	278	1134
HCC-B+C	8	8	9	11	10	46
HCC-nonBC	26	25	40	49	75	215

Gender: 2000-2005 vs. 1981-1985 p=0.0003; 2000-2005 vs. 1986-1990 p≤0.0001; 2000-2005 vs. 1991-1995 p=0.1330; 2000-2005 vs. 1996-2000 p=0.0197. Age: 2000-2005 vs. 1981-1985 p≤0.0001; 2000-2005 vs. 1986-1990 p≤0.0001; 2000-2005 vs. 1991-1995 p≤0.0001 and 2000-2005 vs. 1996-2000 p=0.0292. IQR, interquartile range.

Laboratories) and HCV-RNA detected by polymerase chain reaction (PCR), whereas diagnosis of chronic HBV infection was based on the presence of hepatitis B surface antigen (HBsAg) (enzyme-linked immunosorbent assay; Abbott Laboratories).

Statistical analysis. The data were analyzed by the Mann-Whitney test for the continuous ordinal data between two qualitative variables. The standard deviation was calculated based on the binomial model for the response proportion. $P<0.05$ was considered statistically significant.

Results

Clinical features of the studied patients. A total of 1,807 patients with HCC were diagnosed at our hospital from 1981 to 2005. There were 1,347 male (75%) and 460 female (25%) patients, with a median age of 64 years. The proportion of patients diagnosed as HCC-B (HBV-associated: HBsAg positive, HCVAb negative) was 23% (412 of 1,807), whereas 63% (1,134 of 1,807) had HCC-C (HCV-associated: HCVAb positive, HBsAg negative) and an additional 3% (46 of 1,807) had HCC associated with both viruses. The remaining 215 patients (12%) showed both of the virus markers negative.

As shown in Table I and Fig. 1, the number and proportion of HCC-B cases decreased from 1986 to 1990 and thereafter stabilized, whereas those of HCC-C reached the peak in the period 1996-2000 and thereafter decreased. The number and proportion of the HCC-nonBC (HBsAg and HCVAb negative) cases continued to increase in the whole period.

Background features for patients with HCC. Fig. 2 shows the median age at diagnosis of HCC-B, HCC-C and HCC-nonBC in five-year intervals (1981-1985, 1986-1990, 1991-1995, 1996-2000 and 2001-2005). The median age of patients at diagnosis of HCC-C showed a steadily significant increase from 58 to 69 years of age during the period. The median age of patients with HCC-B and HCC-nonBC did not significantly change during the period.

Fig. 3 shows the age distribution of patients with HCC-B and HCC-C with the five 5-year intervals. There was no difference in the age distribution of patients with HCC-B during these periods. In contrast, HCC-C obviously had a trend to increase in the number of patients aged >65 years.

Table I shows that the male/female ratio of HCC patients decreased from 4.2 in the period 1981-1985 to 2.1 in 2001-2005, indicating clearly the increase of female patients. In analysis of patients in HCC-C, the male/female ratio in the periods 1981-1985, 1986-1990, 1991-1995, 1996-2000 and 2001-2005 were 6.4, 4.8, 2.5, 2.7 and 1.9, respectively (1981-1985 vs. 2001-2005, p≤0.0001) (Table II). The ratio became clearly smaller, indicates an increase in female patients with HCC-C. On the other hand, the male/female ratio of other types of HCC patients did not significantly change during the period.

Discussion

This was a two major liver center-based study designed to examine the sequential change in the background of HCC patients during the past 25 years, 1981-2005. More than 80% of our patients had chronic HBV or HCV infections. During the observation period, the number and proportion of HCC-B cases decreased in the period 1986-1990 and thereafter reached a plateau, whereas HCC-C reached a peak in the period 1995-2000 and thereafter slightly decreased. On the other hand, the number and the proportion of HCC-nonBC gradually increased in the periods of 1981-1985, 1986-1990, 1991-1995, 1996-2000 and 2001-2005 being 26 (11%), 25 (8%), 40 (11%), 49 (12%) and 75 (16%), respectively. Previous studies from Japan reported that the proportion of HCC-C had been increased and reached a plateau in the

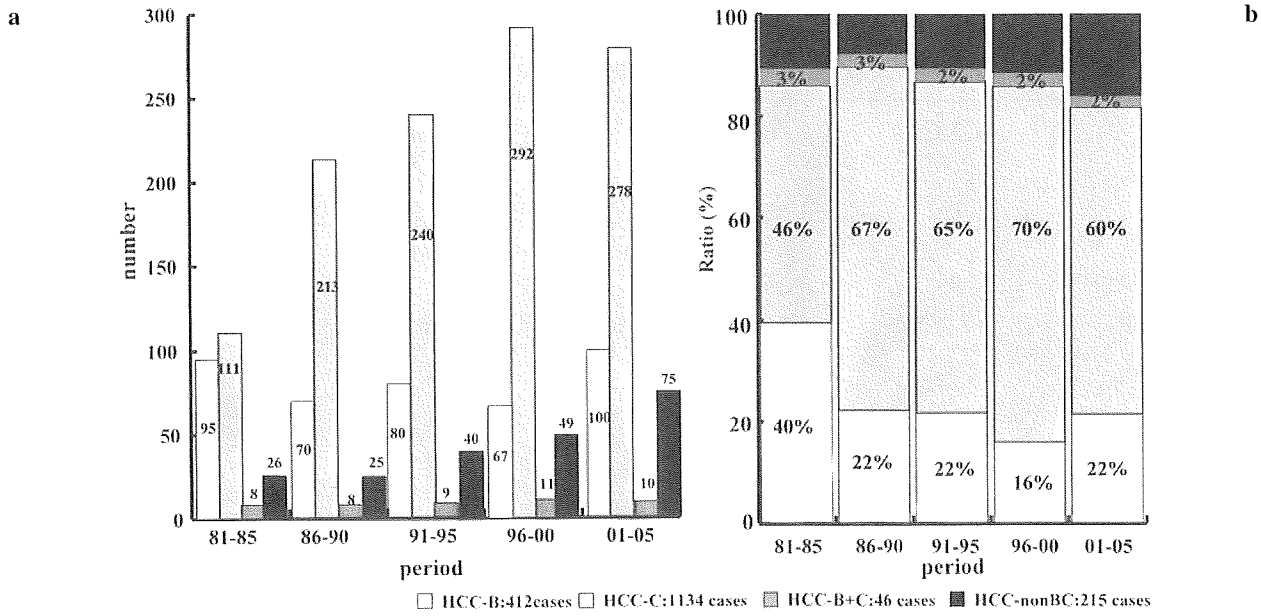

Figure 1. Sequential changes in the number (a) and ratio (b) of HCC patients categorized by etiology during the period 1981-2005 with 5-year intervals.

Table II. The number and male/female ratio of HCC patients during the period of 1981-2005.

Period	1981-1985	1986-1990	1991-1995	1996-2000	2001-2005	Total
Number	240	316	369	419	463	1807
Total						
Male	194	257	268	314	314	1347
Female	46	59	101	105	149	460
Ratio (male/female)	4.2	4.4	2.7	3.0	2.1	2.9
HCC-B						
Male	69	54	61	55	74	313
Female	26	16	19	12	26	99
Ratio (male/female)	2.7	3.4	3.2	4.6	2.9	3.2
HCC-C						
Male	96	176	172	212	182	838
Female	15	37	68	80	96	296
Ratio (male/female)	6.4	4.8	2.5	2.7	1.9	2.8
HCC-nonBC						
Male	21	20	29	40	51	1347
Female	5	5	11	9	24	460
Ratio (male/female)	4.2	4.0	2.6	4.4	2.1	2.9

HBV and nBnC: NS. HCV: 2000-2005 vs. 1981-1985 p≤0.0001; 2000-2005 vs. 1986-1990 p≤0.0001; 1996-2000 vs. 1981-1985 p=0.0033; 1996-2000 vs. 1986-1990 p=0.0084; 1991-1995 vs. 1981-1985 p=0.0024 and 1991-1995 vs. 1986-1990 p=0.0058.

period of 1981-2001 (8,15,17-19). However, in our study, the number and proportion of HCC-C cases decreased in the period 2001-2005. This may be due to interferon therapy associated with a decreased incidence of HCC (20-24). Iron depletion for chronic hepatitis C patients is a promising modality for lowering the risk of progression to HCC (25,26). Oral supplementation with oral branched-chain amino acids has been useful in the prevention HCC (27). Finally, the chronically HCV-infected population is aging in Japan. Yoshizawa reported that age-specific prevalence for the presence of HCVAb among ~300,000 voluntary blood donors from Hiroshima in 1999 clearly increased with the

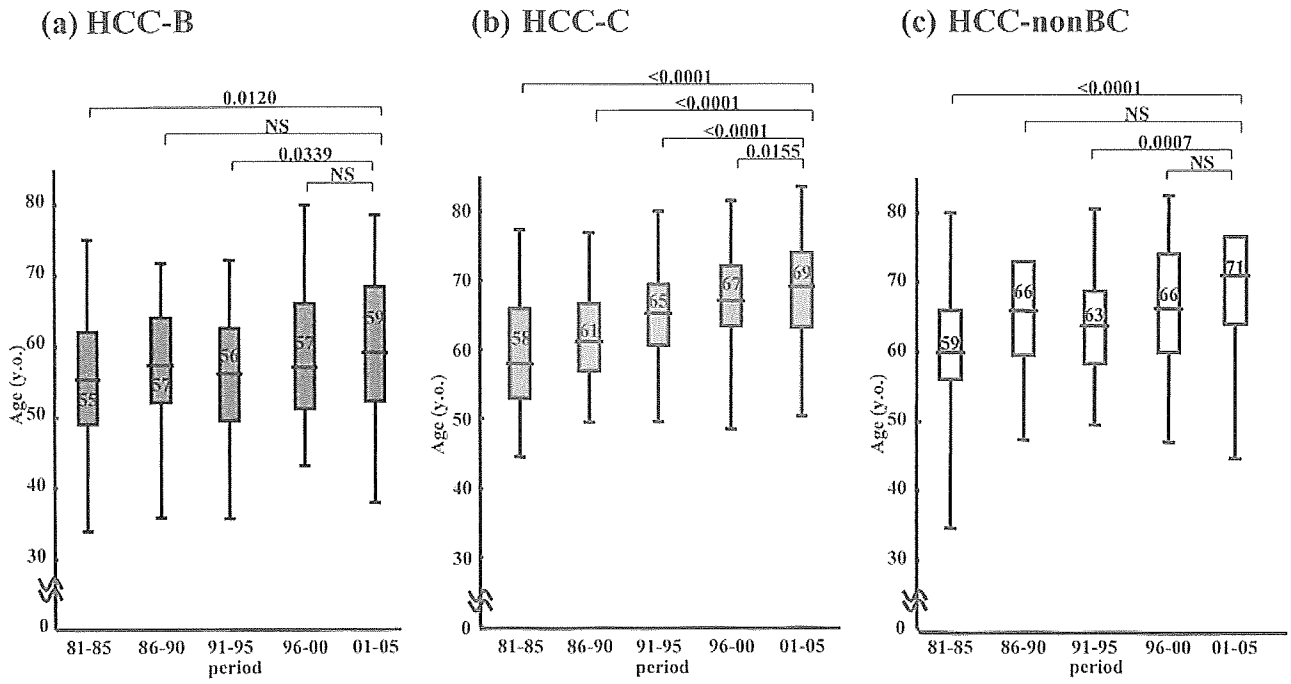

Figure 2. Sequential changes in the median age of HCC patients categorized by etiology during the period, 1981-2005 with 5-year intervals. (a) HCC-B, (b) HCC-C and (c) HCC-nonBC type $p<0.05$.

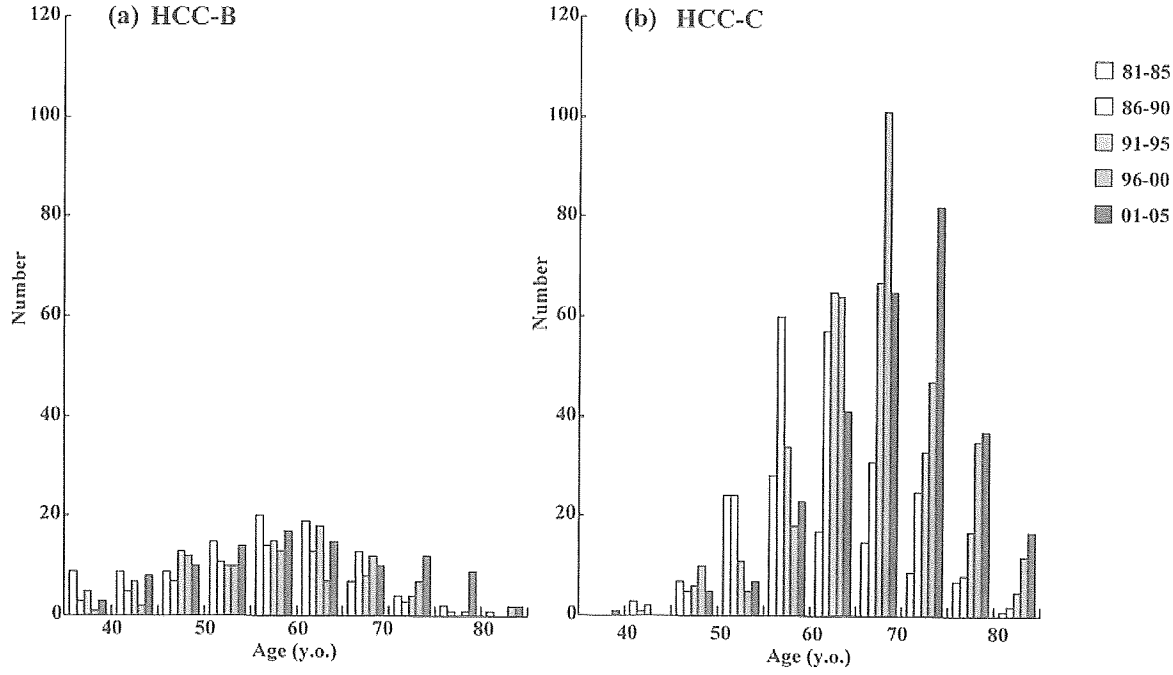

Figure 3. Changes in the age distribution of patients with HCC-B and HCC-C during the period, 1981-2005 with 5-year intervals.

age, reaching the highest proportion of 7% in individuals who were >70 years old (15,16). In this study, the median age of patients with HCC-C steadily increased from 58 to 69 years of age during the studied period. *i.e.* HCV infected people become older and they were regarded as a high risk for HCC.

In almost all populations, males have higher liver cancer proportions than females, with the male/female ratios usually averaging between 2:1 and 4:1 (7). However, the male/female ratio of HCC in Japan was 4.5 in the period 1983-1985 and 2.57 in 2000-2001 (17). In analysis of background features among HCC patients, HCC-B and HCC-nonBC cases revealed no significant change, whereas the male/female ratio of patients with HCC-C steadily decreased from 6.4 to 1.9 during the period. We suggest that the increase of female

patient with HCC-C was caused by the aging of HCV infected people. The increase of females among HCC patients was considered to increase because of HCC-C.

It is known that 2 to 4 decades of chronic HCV infection are required to develop cirrhosis and subsequent HCC (28-31). The number of HCC cases has increased in Japan, because individuals infected with HCV in the past have grown old and have reached the cancer-bearing age. The prevalence of HCV infection in young Japanese individuals is low and the incidence of HCVAb is very low because of preventative actions against HCV infection such as the screening of blood products for HCV and the use of sterile medical equipment (32). Additionally, we showed that the number and proportion of patients with HCC-C cases decreased together with an increase in the median age, whereas the number and ratio of HCC-nonBC steadily increased during the studied period. Based on these findings it may be expected that the incidence of HCC-nonBC in Japan may continue to increase even after the consequence of the HCV epidemic level off in the near future, although Japan is far advanced with regard to HCC-C.

In summary, HCC patients rapidly increased from 1981 to 2000 and this increase originated from HCC-C and the increase of the median age and the number of female patients with HCC-C. Increase in the number and proportion of the HCC-nonBC patients are also significant.

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ORIGINAL ARTICLE

Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study

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Abstract We prospectively compared allogeneic hematopoietic stem cell transplantation (allo-HSCT) with chemotherapy as a post-remission therapy in a multicenter trial (JALSG AML97) of adult patients with intermediate or poor risk acute myeloid leukemia (AML). Of 503 patients aged 15–50 years old registered between December 1997 and July 2001, 392 achieved complete remission (CR). CR patients classified in the intermediate or poor risk group using a new scoring system were tissue typed. Seventy-three with and 92 without an HLA-identical sibling were assigned to the donor and no-donor groups. Of 73 patients in the donor group, 38 (52%) received allo-HSCT during CR1 and 17 (23%) after relapse. Intention-to-treat analysis revealed that the relapse incidence was reduced in the donor group (52 vs. 77%; $p = 0.008$), and the disease-free survival (DFS) improved (39 vs. 19%; $p = 0.016$), but overall survival (OS)

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was not significantly different (46 vs. 29%; $p = 0.088$). The OS benefit was seen in the patients aged 36–50 years old (49 vs. 24%; $p = 0.031$), suggesting an advantage of allo-HSCT among older patients with leukemia that is more resistant to chemotherapy than that among younger patients.

Keywords AML · Allogeneic hematopoietic stem cell transplantation · Post-remission chemotherapy

1 Introduction

Around 70–80% of newly diagnosed patients with adult acute myeloid leukemia (AML) achieve complete remission (CR) when treated with cytarabine (AraC) and anthracycline, usually daunorubicin (DNR) or idarubicin (IDR). However, only about one-third of these patients remain disease free for more than 5 years [1–5]. Intensified post-remission chemotherapy has improved the survival rates of patients with AML, especially of younger patients [6]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered to be the most intensive post-remission treatment consisting of high-dose chemoradiotherapy and allo-immune mechanisms. However, the powerful anti-leukemic effects of this treatment are counterbalanced by a high incidence of treatment-related mortality (TRM). Thus, allo-HSCT has not always been considered superior to chemotherapy [7, 8]. Intensified chemotherapy with high-dose Ara-C confers promising results on good risk patients [9] for whom allo-HSCT is currently abstained in the first CR (CR1). The Japan Adult Leukemia Study Group (JALSG) AML97 protocol committee circulated a questionnaire among the institutions participating in JALSG regarding their policy about indications for allo-HSCT among AML patients in CR1. The findings revealed that good risk patients in CR1 did not undergo an allo-HSCT at most of these institutions. Cytogenetic profile has been widely used to classify the patients with AML [7–13]; however, cytogenetic studies are not always foolproof. The JALSG established a scoring system that adopted significant factors including cytogenetic results from previous JALSG AML trials [14]. We applied this scoring system to stratify patients and conducted a prospective, multicenter cooperative study (AML97) to compare allo-HSCT with chemotherapy among intermediate and poor risk patients with AML in CR1.

2 Patients and methods

2.1 Patients and study design

The JALSG AML97 study was implemented between December 1997 and July 2001 at 103 institutions where the ethical committees approved the protocol. Adult patients aged from 15 to 64 years newly diagnosed with de novo AML according to the French–American–British (FAB) classification at each institution were eligible, but those with acute promyelocytic leukemia (APL) were excluded. Peripheral blood and bone marrow smears of the registered patients were stained with May-Giemsa, peroxidase, and esterase at Nagasaki University and subsequently reviewed by a central review committee. All patients provided written informed consent to participate before registration in this study.

The chemotherapeutic design of AML97 has been described elsewhere in detail [15]. In short, all the patients were treated with the same induction therapy consisted of AraC (100 mg/m^2, continuous infusion, days 1–7) and IDR (12 mg/m^2 days 1–3). If the patients did not achieve remission after the first induction therapy, then the same therapy was given again. For patients who did not achieve a CR even after second induction therapy, no further treatment was defined in this study. In the comparison between allo-HSCT and chemotherapy as post-remission therapy, these patients were not included in the analysis. All patients who achieved CR were randomized to receive either 4 courses of consolidation therapy without maintenance therapy (group A) or the conventional JALSG post-remission regimen with maintenance therapy (group B) [3]. The results of the two post-remission chemotherapeutic strategies (group A vs. group B) were comparable [15]. The CR patients were classified into good, intermediate or poor risk groups according to the scoring system described below. Intermediate or poor risk patients younger than 50 years old with living siblings were tissue typed. Patients with an HLA-identical sibling were assigned to undergo allo-HSCT soon after three courses of consolidation therapy (donor group), and those without living or HLA-identical siblings were assigned to the no-donor group that continued receiving chemotherapy.

Patients in the donor group with AST or ALT values fourfold higher than the normal range, serum bilirubin and creatinine more than 2 mg/dl, ejection fraction based on an echocardiogram of less than 50% or oxygen saturation according to pulse oximetry of less than 90% were ineligible for allo-HSCT, but were analyzed as a donor group one in an intention-to-treat fashion. Conditioning before transplantation and prophylaxis for graft-versus-host disease was performed according to each institutional standard. Either allogeneic peripheral blood or bone marrow was allowed to be the stem cell source.

2.2 Scoring system

We collected clinical and laboratory data (except for APL) from previous JALSG AML trials (AML87, $n = 234$

Table 1 JALSG scoring system

Scoring system		
System 1		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	$\leq 2 \times 10^9$/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
No. of induction	1	+1
t(8;21) or inv(16)	+	+1
Total score		
Good risk group		8–10
Intermediate risk group		5–7
Poor risk group		0–4
System 2		
MPO positive blasts	>50%	+2
Age	≤50 years	+2
WBC	$\leq 2 \times 10^9$/l	+2
FAB subtypes	non-M0, M6, M7	+1
Performance status	0, 1, 2	+1
Total score		
Good risk group		7–8
Intermediate risk group		4–6
Poor risk group		0–3

MPO myeloperoxidase, *WBC* white blood cell

patients; AML89, $n = 311$; AML92, $n = 986$), and then selected significant factors for achieving CR, disease-free survival (DFS) and overall survival (OS) using multivariate analysis [14]. According to the weight of significance, myeloperoxidase positivity of blasts, patient age, and WBC count at diagnosis were valued at 2 points, and FAB subtypes, performance status, numbers of inductions required to achieve CR, and favorable karyotypes of t(8;21) or inv(16) were valued at 1 point (Table 1, system 1). When we originally planned to use this system, cytogenetic data were not always available at diagnosis. Thus, we designed the system 2 that could be applied even without a cytogenetic data.

2.3 Statistical analysis

The aim of this study was to compare the efficacy of allo-HSCT and chemotherapy as a post-remission treatment, by evaluating DFS and OS rate. Forty-two patients were estimated for an evaluation of the primary endpoint of this study. The JALSG data management committee collected the clinical data from all participating institutions, then fixed them and analyzed the OS of each risk group in July 2004 and the relapse rate (RR), DFS, OS and TRM of the donor and no-donor groups in January 2009. The OS, DFS, RR and TRM were measured from the date of CR. The event for OS was death due to all causes, and patients were censored at the last observation date if alive. The events of DFS were death during CR or relapse. The RR was defined as the cumulative probability of relapse, censoring at death in CR. The events of TRM comprised death before relapse. We estimated OS, DFS, RR and TRM with their respective standard errors using the Kaplan–Meier method [16]. We compared the OS, DFS, RR and TRM between the patients with and without a donor using the log-rank test. Furthermore, the hazard ratio and the 95% confidence interval (CI) of the OS, DFS, RR and TRM were calculated using Cox regression analysis. The Wilcoxon rank-sum test was used for the continuous data, such as age and WBC count, while the Chi-square test was used for the ordinal data, such as the risk group and the frequency of allo-HSCT. All analyses were performed on the intention-to-treat principal with all patients in their allocated arms. Adding to the prospective comparison of the efficacy between allo-HSCT and chemotherapy, we also retrospectively performed subgroup analysis by age. Statistical analyses were conducted using the SAS software package (SAS Institute, Inc, Cary, NC).

3 Results

3.1 Study patients and genetical allocation

Five hundred and three de novo AML patients aged from 15 to 50 years participated in the AML97 comparison of allo-HSCT with chemotherapy as a post-remission therapy. Of 392 patients achieved CR, 62 patients were excluded from the analysis because of insufficient data mainly deficient clinical data at diagnosis which were essential to verify their classification. Three hundred and thirty evaluable patients were classified into the good ($n = 149$), intermediate ($n = 162$) or poor risk ($n = 19$) groups using the scoring system described above (Fig. 1). The 5-year OS

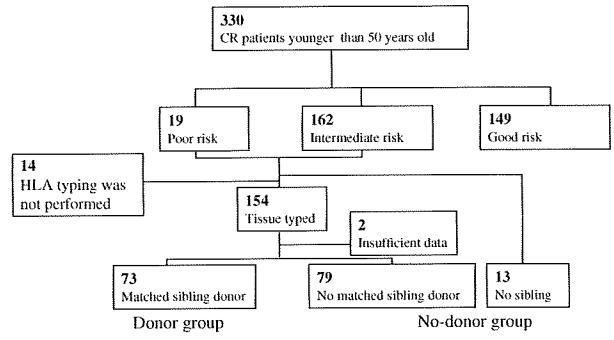

Fig. 1 Overview of patients included in analysis by risk classification, HLA typing, and donor availability

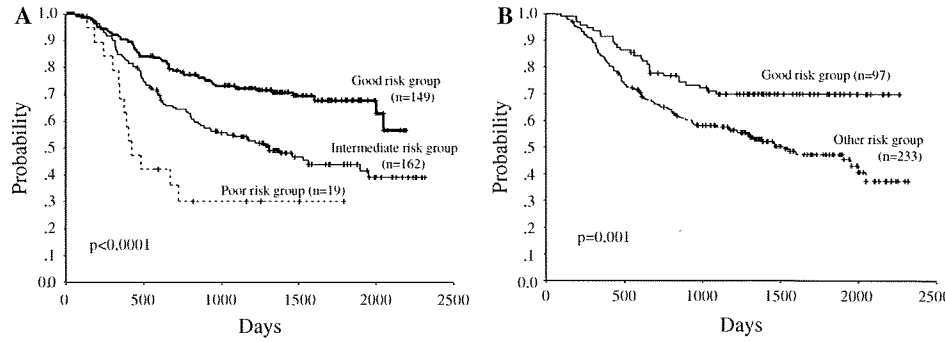

Fig. 2 Overall survival of patients in CR according to JALSG scoring system (**a**) and by cytogenetic studies (**b**)

rates of the CR patients with good, intermediate and poor risk were 68, 44 and 30%, respectively [hazard ratio (HR), 0.51 (good vs. intermediate) and 0.25 (good vs. poor), respectively; 95% confidential interval (CI), 0.35–0.73 (good vs. intermediate) and 0.14–0.48 (good vs. poor); $p < 0.0001$; Fig. 2a]. Among the intermediate and poor risk patients with living siblings, 154 patients and their siblings were examined for their HLA types. Seventy-three of these patients had an HLA-identical sibling and were assigned to the donor group. Thirteen patients with no siblings and 79 patients without an HLA-identical sibling were assigned to the no-donor group (92 patients). Finally, one patient in donor group and one patient in no-donor group were excluded from the analysis because of their insufficient data of survival (Fig. 1). The follow-up durations of the donor and no-donor groups were 1854 days (range 163–3176 days) and 1010 days (range 93–3008 days), respectively.

3.2 Patient characteristics of donor versus no-donor groups

Table 2 shows the characteristics of patients in the donor and no-donor groups. The distributions of these features were comparable in both groups with respect to age, gender, initial WBC count, MPO positivity of blasts, FAB subtype, performance status, prognostic risk according to JALSG score, presence of favorable cytogenetic abnormalities, and the groups of post-remission chemotherapy.

3.3 Donor group

Fifty-six patients (76%) in the donor group actually underwent allo-HSCT (Table 2). Thirty-eight patients (52%) received an allo-HSCT during CR1 at a median of 159 days (range 43–314 days) from CR1. Eighteen patients underwent allo-HSCT after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 183 days (range 39–757 days) and 248 days (range 157–973 days), respectively. Thirty and 24 patients were transplanted after undergoing a conditioning regimen with or without total body irradiation (TBI), respectively, and conditioning information was not available for 2 patients. The sources of transplanted stem cells were bone marrow cells ($n = 26$), peripheral blood cells ($n = 27$) and bone marrow cells together with peripheral blood cells ($n = 2$). Twenty-nine of the 56 patients in the donor group who underwent allo-HSCT remain alive. Twenty patients died of recurrent leukemia and 7 of transplant-related causes. Seventeen patients allocated to the donor group did not receive a transplantation for the following reasons; patients' refusal ($n = 6$), donors' refusal to donate ($n = 2$), physician's decision ($n = 1$), disease progression before transplantation ($n = 2$), donor health problems ($n = 2$) and unknown reasons ($n = 4$).

3.4 No-donor group

Of the 92 patients in the no-donor group, 42 eventually underwent HSCT (Table 2): autotransplantation ($n = 3$), allo-HSCT from HLA mismatched-related donors ($n = 4$), allo-HSCT from an HLA matched-unrelated donor ($n = 28$), and allo-HSCT from an HLA-mismatched unrelated donor ($n = 7$). Eleven patients underwent a transplantation during CR1 from an unrelated donor or mismatched-related donor at a median of 281 days (range 170–1700 days) from CR1, significantly later than those transplanted during CR1 in the donor group ($p < 0.001$). Thirty-one patients received a transplantation after relapse. The median times between CR1 and relapse and between CR1 and a transplantation were 329 days (range 92–876 days) and 519 days (range 167–1373 days), respectively.

3.5 Comparison of donor versus no-donor groups

The actual risk of relapse at 8 years was significantly lower in the donor group than in the no-donor group (52 vs. 77%, respectively, HR, 0.58; 95% CI, 0.39–0.88; $p = 0.008$; Table 3). The TRM did not significantly differ between the donor and the no-donor groups (16 vs. 17%, respectively, HR, 0.97; 95% CI, 0.34–2.80; $P = 0.959$; Table 3). Seven

Table 2 Patients' characteristics

	Donor	No-donor	*p*
Total number	73	92	
Age			
Median (range)	37 (16–50)	36 (15–50)	0.60[a]
15–35 years	33	46	
36–50 years	40	46	0.54[b]
Sex			
M/F	44/29	45/47	0.15[b]
WBC at diagnosis (10^9/l) (range)	3.8 (0.05–36.8)	5.1 (0.14–45.0)	0.16[a]
MPO positivity of blasts (range)	30 (0–100)	50 (0–100)	0.18[a]
FAB classification			
M0	4	6	
M1	18	25	
M2	22	24	
M4	20	23	
M5	7	14	
M6	1	0	
M7	1	0	0.67[b]
Performance status			
0–1	66	84	
2–3	7	8	0.70[b]
Risk classification by JALSG scoring system			
Intermediate	64	84	
Poor	9	8	0.45[b]
Cytogenetics			
t(8;21) or inv(16)	4	4	0.74[b]
Chemotherapy group			
Group A	38	42	
Group B	30	47	0.28[c]
Not randomized	5	3	
Allogeneic transplant			
During CR1	38	11	
		9 from UD	
		1 from MUD	
		1 from MRD	
After relapse	18	31	
No transplant	17	50	

UD HLA-matched unrelated donor, *MUD* HLA-mismatched unrelated donor, *MRD* HLA-mismatched related donor, *WBC* white blood count, *MPO* myeloperoxidase

[a] Mann–Whitney test

[b] Chi-square test

[c] Chi-square test excluding non-randomized

patients in the donor group and four in the no-donor group died of transplant-related causes during CR1. The lower RR in the donor group resulted in a significantly better DFS compared with the no-donor group (39 vs. 19%, respectively, HR, 0.63; 95% CI, 0.44–0.92; $P = 0.016$; Table 3; Fig. 3). The significant superiority of DFS in the donor group translated into a higher OS rate, but the difference in OS between the two groups did not reach statistical significance (46 vs. 29%, HR, 0.70; 95% CI, 0.47–1.06; $p = 0.088$; Table 3; Fig. 4).

The donor/no-donor analysis was performed on the intention-to-treat principal, which may underestimate the beneficial effect of allo-HSCT probably because of low compliance of transplantation. The 8-year DFS and OS of the recipients actually transplanted during CR1 ($n = 38$) in the donor group were significantly better than those of the patients not transplanted in the no-donor group ($n = 50$); 58 versus 27%, HR, 0.36; 95% CI, 0.20–0.66; $p < 0.001$, and 61 versus 24%, HR, 0.36; 95% CI, 0.19–0.68; $p = 0.001$, respectively.

Table 3 Effects of donor availability on outcome in donor and no-donor groups

Outcome	Donor			No-donor			*p*	HR (95% CI)
	n	No. of events	Probability of outcome at 8 years ±SE (%)	*n*	No. of events	Probability of outcome at 8 years ±SE (%)		
All patients	73			92				
RR		36	52 ± 6		67	77 ± 5	0.008	0.58 (0.39–0.88)
TRM		7	16 ± 6		7	17 ± 7	0.959	0.97 (0.34–2.80)
DFS		44	39 ± 6		74	19 ± 4	0.016	0.63 (0.44–0.92)
OS		37	46 ± 7		61	29 ± 6	0.088	0.70 (0.47–1.06)
Age ≤35	33			46				
RR		17	52 ± 9		31	70 ± 7	0.309	0.74 (0.41–1.33)
TRM		2	12 ± 8		3	15 ± 8	0.785	0.78 (0.13–4.71)
DFS		20	39 ± 9		34	26 ± 7	0.366	0.78 (0.45–1.35)
OS		18	42 ± 10		27	35 ± 9	0.860	0.95 (0.52–1.72)
Age >35	40			46				
RR		19	52 ± 9		36	85 ± 6	0.006	0.46 (0.26–0.81)
TRM		5	19 ± 8		4	19 ± 11	0.962	1.03 (0.27–3.92)
DFS		24	39 ± 8		40	12 ± 5	0.012	0.52 (0.31–0.87)
OS		19	49 ± 9		34	24 ± 7	0.031	0.54 (0.31–0.95)

RR relapse rate, *DFS* disease-free survival, *TRM* treatment-related mortality, *OS* overall survival

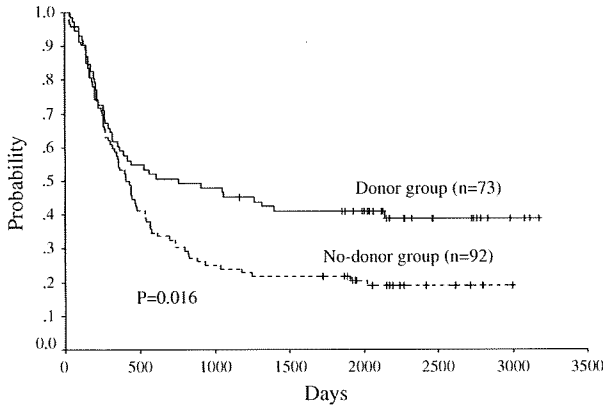

Fig. 3 Disease-free survival in donor and no-donor groups

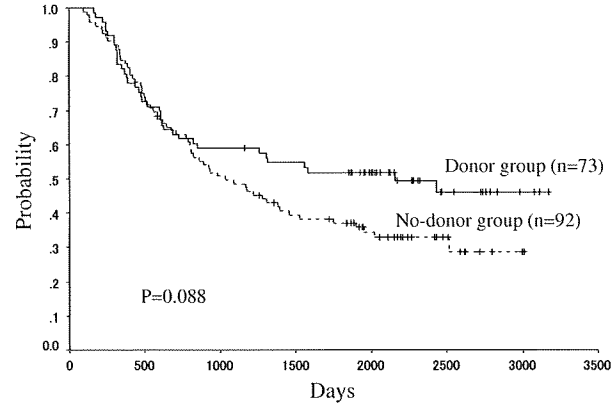

Fig. 4 Overall survival in donor and no-donor groups

3.6 Subset analysis according to patient age

The OS of the patients younger than 35 years of age were comparable between the donor and the no-donor groups (Fig. 5a). However, the OS of the patients aged >35 in the donor group was significantly better compared with the no-donor group (49 vs. 24%, respectively, HR, 0.54; 95% CI, 0.31–0.95; $p = 0.031$; Table 3; Fig. 5b). The RR, TRM, DFS and OS in the donor group were comparable between the two age categories (Table 3; Fig. 5c). In contrast, OS and DFS were marginally worse in the no-donor group of patients aged >35 than ≤35 years (Table 3; Fig. 5d). The distribution of the cytogenetic profile, risk by the JALSG scoring system, myeloperoxidase positivity of blasts, WBC count, FAB classification and performance status at diagnosis did not significantly differ between the two age categories in the no-donor group (data not shown).

4 Discussion

Many clinical trials have compared allo-HSCT with chemotherapy as a post-remission therapy for the patients with AML during CR1. Most of these targeted all patients in CR1 as a single population without prospective stratification by the prognostic factors. Thus, patients were simply assigned into the allo-HSCT or the chemotherapy groups according to donor availability [7, 10, 17, 18]. Here, we

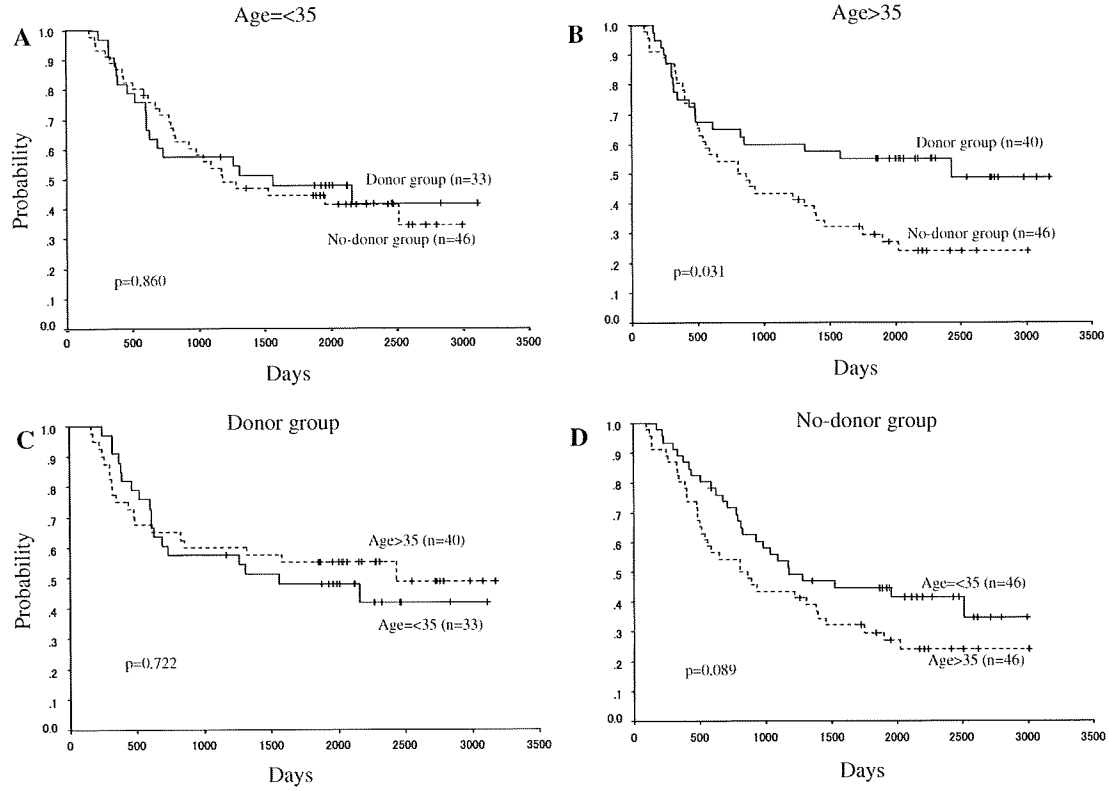

Fig. 5 Overall survival of patients according to age (**a** and **b** ≤35 and >35 years, respectively) and donor availability (**c** and **d**, donor and no-donor groups, respectively)

prospectively compared the effectiveness of allo-HSCT with chemotherapy among patients who were stratified into intermediate or poor risk groups according to JALSG scoring, which constitutes a new means of predicting the prognosis of AML. When this study was planned, as the availability of the cytogenetic study was expected to be variable, and the JALSG scoring system was revealed to be useful to stratify the patients, we adopted a scoring system to select the intermediate and poor risk patients. In contrary to our expectation, cytogenetic studies were performed in 99.2% of the registered patients and the results were available in 97% of the patients. Of 330 CR patients younger than 50 years old, cytogenetic studies disclosed that 97 had good prognostic chromosomal abnormalities, i.e., t(8;21) or inv(16). The OS was significantly better among patients with than without good prognostic cytogenetic profiles (70 vs. 47% at 5 years, with HR, 0.51; 95% CI, 0.34–0.77; $p = 0.001$; Fig. 2b). According to JALSG scoring, 87, 10 and 0 patients with good prognostic cytogenetic abnormalities corresponded to the good, intermediate and poor risk groups, respectively. More good risk patients were selected using this scoring system than by that using karyotype of AML cells alone and about 10% of patients who might be classified into the good risk group by cytogenetic profiles entered the comparison groups by the JALSG scoring system. The JALSG scoring system, which resembles the index used in the Bordeaux Grenoble Marseille Toulouse (BGMT) intergroup study [18], obviously separated patients with a good prognosis who should be excluded from the transplantation trials.

Allo-HSCT prevents AML relapse through intensive cytoreduction using high-dose chemoradiotherapy and graft-versus-leukemia effects. However, previous trials have not always shown advantages of this strategy on the survival of AML patients in CR1. Some studies have not found a benefit of allo-HSCT either on DFS or OS [7, 8], and some showed an advantage only on DFS [10, 17] compared with chemotherapy/auto-transplantation. Retrospective subgroup analysis and meta-analysis have shown a better OS in the donor group [10, 13, 19, 20], demonstrating the importance of limiting the indication of allo-HSCT for only the patients with an intermediate or poor risk.

The following issues should be considered regarding the prospective comparison of allo-HSCT with chemotherapy: assignment of patients according to sibling donor availability [21], low compliance of allo-HSCT for patients in the donor group, and allo-HSCT performed in the no-donor

group from unrelated donors. We could compare the effectiveness of treatment strategies using the intention-to-treat analysis. However, the intrinsic issues of this type of trial and recent advances in alternative stem cell sources will cause difficulties with future prospective comparison of allo-HSCT and chemotherapy using a similar study design.

Although the comparison was performed among patients in the intermediate and poor risk groups, the benefit of allo-HSCT was not significant in OS. Low compliance of allo-HSCT during CR1 in the donor group (52% in the current trial) and allo-HSCT in the no-donor group (total 45%; 11% during CR1) appeared to make the efficacy of allo-HSCT underestimated, especially with regard to OS. However, survival was significantly better among older patients in the donor group (Table 3; Fig. 5b), which seemed to contradict previous findings [19]. Age usually adversely affects allo-HSCT outcome, but it was not associated with the decrease of OS in the donor group in the present study (Table 3; Fig. 5c). Low incidence of TRM probably allowed the powerful anti-leukemic effect of allo-HSCT to function properly, indicating the advantage of allo-HSCT especially among older patients with leukemia that was more resistant to chemotherapy than that among younger patients [1] shown in the no-donor group (Fig. 5d), and caused a contrary result from HOVON/SAKK study. The recent reduction in TRM seemed to contribute much to these results as suggested by others [22, 23]. Different population of the cohorts selected by JALSG scoring and by cytogenetic profiles might also have influenced the present findings.

Molecular markers can be very useful for selecting patients who will most likely benefit from allo-HSCT during CR1 among those with a normal karyotype, which comprises the largest group of patients with AML [24]. The overall safety of allo-HSCT obviously needs improvement, and also patients with chemotherapy-resistant AML who could benefit from allo-HSCT should be identified. Thus, stratification of patients with AML should be improved using a combination of leukemic cell karyotype and, genetic markers and also other clinical findings.

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Relationship between monoclonal gammopathy of undetermined significance and radiation exposure in Nagasaki atomic bomb survivors

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Radiation exposure is a possible predisposing factor for monoclonal gammopathy of undetermined significance (MGUS), but the association has been uncertain. We investigated the relationship between radiation exposure and MGUS prevalence by using data from the M-protein screening for Nagasaki atomic bomb survivors between 1988 and 2004. Radiation exposure was assessed by exposure distance from the hypocenter and exposure radiation dose. We computed prevalence ratios (PRs) and the 95% confidence intervals (CIs) adjusting for exposure age and sex. A total of 1082 cases of MGUS were identified from 52 525 participants. MGUS prevalence was significantly higher in people exposed at distance within 1.5 km than beyond 3.0 km (PR, 1.4; 95% CI, 1.1-1.9) among those exposed at age 20 years or younger, but it was not found among those exposed at age 20 years or older. MGUS prevalence was also significantly higher in people exposed to more than 0.1 Gy than those exposed to less than 0.01 Gy (PR, 1.7; 95% CI, 1.0-2.8) among those exposed at age 20 years or younger. Thus, people exposed at younger age exhibited a significantly high risk of MGUS when exposed to a high radiation dose. There was no clear association between radiation exposure and the malignant progression of MGUS. Further detailed analysis is needed. (Blood. 2009;113:1639-1650)

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder, which is defined by a serum monoclonal protein (M-protein) concentration of 3 g/dL or less, 10% or fewer plasma cells in the bone marrow, and the absence of anemia, osteolytic lesions, hypercalcemia, and renal dysfunction.[1] Although the majority of patients with MGUS remain stable for prolonged periods, malignant transformation to multiple myeloma occurs at a constant rate of 1% per year.[2] Given that myeloma is an incurable hematologic malignancy, it is important to elucidate etiology and predisposing factors of MGUS.

Etiologic factors for MGUS have not been investigated fully.[3-5] There are currently no consistent risk predictors beyond age, sex, and race for developing MGUS. Although radiation exposure is well known to initiate leukemogenesis, there have been conflicting reports about the association between radiation exposure and plasma cell disorders.[6-11] An Italian case reference study reported an increased risk of MGUS among people exposed to occupational radiation exposure.[12] However, a small survey for atomic bomb survivors showed no association between radiation dose and the relative risk of MGUS.[13] Sample sizes of these previous studies were too small to obtain reliable results for association between radiation exposure and incidence of the disease.

We have recently reported the age-specific MGUS prevalence in the Japanese population, indicating 2.4% in those older than 50 years.[14] The report used an M-protein screening data from approximately 52 000 atomic bomb survivors but did not report the relationship between radiation exposure and MGUS risk. The large number of study participants from the radiation-exposed population could provide a great opportunity to investigate the relationship between radiation exposure and the risk of MGUS. Our preliminary analysis observed that MGUS risk was higher in those exposed to higher radiation at a young age.[15] However, the preliminary observation lacked detailed analyses for the relationship and did not include clinical characteristics. In the present study, we performed comprehensive analyses for the screening data by considering distance from the hypocenter of the nuclear explosion, radiation dose, age at exposure, age at diagnosis, and M-protein level to elucidate whether radiation exposure is related with the development of MGUS and the progression.

Methods

Data source

Screening for M-protein was initiated in October 1988 for atomic bomb survivors at the Health Management Center of Nagasaki Atomic Bomb Casualty Council, where a comprehensive medical check-up has been offered twice a year since 1968; several cancer screenings have been

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